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1685 ANNOUNCEMENTS

Anticipatory Vomiting in Women Receiving Cyclophosphamide, Methotrexate, and 5-FU (CMF) Adjuvant Chemotherapy for Breast Carcinoma[1,2]

Patti M. Wilcox,[3,*] John H. Fetting,[3] Kathleen M. Nettesheim,[4] and Martin D. Abeloff[3]

To determine the incidence of anticipatory vomiting (AV) and postchemotherapy nausea and vomiting (PCNV) in women receiving cyclophosphamide, methotrexate, and 5-FU (CMF) adjuvant chemotherapy for breast carcinoma, we studied 52 women randomized to two regimens (standard-dose and low-dose) of CMF. Charts were reviewed for the cycle of onset of AV and PCNV, the severity of PCNV, and relationships of these syndromes to CMF dose and protocol compliance. Among the 52 patients, AV occurred in 17 (33%), while PCNV was experienced by 46 (88%). Severe PCNV (defined as uncontrolled nausea and/or vomiting interfering with performance of daily activities) occurred in 22 of 52 (42%) women. Eighteen of 23 (78%) women receiving standard-dose CMF experienced severe PCNV, and 13 of these had AV. Patients in whom severe PCNV began before cycle 4 were more likely to develop AV than women in whom PCNV began later ($P < 0.01$). Ten of 52 (19%) patients discontinued CMF adjuvant chemotherapy because of nausea and vomiting; seven of the ten (70%) were receiving standard-dose CMF and seven had experienced AV. This study demonstrates that both AV and PCNV are significant toxic effects that not only affect the quality of life of a woman receiving CMF chemotherapy for breast cancer but also limit the ability of the clinician to provide maximum therapy to women at high risk of recurrence of breast carcinoma. [Cancer Treat Rep 66:1601–1604, 1982]

Nausea and vomiting following the administration of cytotoxic agents presumably results from an interaction between an antineoplastic agent and some station along the afferent and efferent reflex arc including the gastrointestinal tract, spinal cord, and brain stem (1,2). Such postchemotherapy nausea and vomiting (PCNV) is a dose-limiting toxic effect of chemotherapeutic agents (3). Recently, another chemotherapy-related nausea and vomiting syndrome, called anticipatory nausea and vomiting, has been reported (4,5). This syndrome is defined as nausea and vomiting prior to, and in anticipation of, chemotherapy administration; its pathogenesis is unknown.

This paper reports the incidence and time of onset of anticipatory vomiting (AV) and PCNV in a series of women with breast carcinoma treated with adjuvant chemotherapy and relates the development of AV to the severity of PCNV. Protocol compliance by the study population affected by AV and PCNV was also analyzed.

MATERIALS AND METHODS

Population Characteristics

The study consisted of a retrospective chart review of 52 patients treated at The Johns Hopkins Oncology Center (JHOC). The patients, a subgroup of a larger community cancer network trial, had undergone radical or modified radical mastectomy for stage II or III breast carcinoma. They were randomly assigned to two regimens of cyclophosphamide, methotrexate, and 5-FU (CMF) given every 28 days for 24 cycles. The purpose of the chemotherapy study was to compare the therapeutic efficacy and toxicity of two CMF regimens: *standard-dose CMF*—100 mg/m^2 of cyclophosphamide orally on Days 1–14, 40 mg/m^2 of methotrexate iv on Days 1 and 8, and 600 mg/m^2 of 5-FU iv on Days 1 and 8; and *low-dose CMF*—40 mg/m^2 of cyclophosphamide orally on Days 1–14, 15 mg/m^2 of methotrexate iv on Days 1 and 8, and 350 mg/m^2 of 5-FU iv on Days 1 and 8. Of the 52 JHOC participants, 23 (44%) were randomized to standard-dose CMF and 29 (56%) to low-dose CMF. No patients received radiotherapy or hormonal therapy during this study.

Twenty-four of the women (46%) were premenopausal and 28 (54%) were postmenopausal, with ages ranging from 29 to 66 years. The 52 JHOC patients did not vary significantly from the total population of 93 women in the community cancer network trial in terms of menopausal status, number of axillary nodes involved with tumor, tumor size, or CMF dose randomization. The study pop-

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[2]Supported in part by Public Health Service grant CA-17448 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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TABLE 1.—AV and CMF dose

Group	No. (%) of patients		
	Total	Without AV	With AV
Standard-dose CMF	22*	9 (41)	13 (59)
Low-dose CMF	29	25 (86)	4 (14)†
Total	51*	34 (67)	17 (33)

*1 patient receiving standard-dose CMF who refused treatment because of severe PCNV after cycle 1, Day 1, could not be categorized as having or not having AV.
†$P < 0.01$.

ulation did differ from the community program group in that the 41 women followed in the community were seen by a physician alone, while only 17 of the 52 JHOC patients (33%) were seen by a physician alone. The remaining 35 women (67%) in the JHOC group were followed in joint practice by a physician and a nurse practitioner (P. M. Wilcox). Thus, many of the JHOC participants were evaluated by two health care providers during their course of therapy. The preliminary results of the entire community cancer network trial are reported elsewhere (6).

Assessment of Nausea and Vomiting

Based on clinical reports, we defined AV as vomiting prior to the administration of CMF adjuvant chemotherapy without a known cause for vomiting (eg, concurrent illness or evidence of metastatic disease). As part of the goal to evaluate CMF toxicity, the principal investigator (M. D. Abeloff) developed guidelines for rating severity of PCNV and for modifying CMF dose accordingly. The grading of PCNV included none, moderate (requiring antiemetics but controllable), and severe (uncontrolled, interfering with performance of daily activities). Severe PCNV required a 50% reduction of CMF dose per protocol. The chart review of the 52 cases was accomplished by recording the date(s) and grade of PCNV and the date(s) of AV from the clinician's narrative record and the computerized protocol symptom list. We related the severity of the PCNV to the development of AV and analyzed the impact of these nausea and vomiting syndromes (PCNV and AV) on protocol compliance. Statistical relationships were calculated using the standard chi-square and two-tailed T tests.

RESULTS

AV occurred in 17 of 52 women (33%). Table 1 demonstrates the relationship between AV and the dose levels of CMF. AV occurred more frequently in women receiving standard-dose CMF than in patients receiving low-dose CMF ($P < 0.01$). PCNV was experienced by 46 of the 52 women (88.5%) in the study. Table 2 shows the incidence of PCNV in relationship to the dose levels of CMF. There is a statistically significant relationship between the incidence of severe PCNV and the higher CMF dose ($P < 0.001$).

The relationship between the severity of PCNV and AV is shown in table 3. All 17 women who developed AV experienced prior PCNV, and 13 of the 17 (76.5%) reported severe PCNV. AV occurred more frequently in women with severe PCNV than in those with moderate PCNV ($P< 0.001$).

The cycle of onset of PCNV was similar for both those women who experienced AV (mean cycle, 2.17; median cycle, 1) and those who did not experience AV (mean cycle, 2.50; median cycle, 2). However, the cycle of onset of severe PCNV varied considerably between the two groups: patients with AV had a mean cycle of onset of 3.46 (median cycle, 3: SE, 0.82) while patients without AV had a mean cycle of onset of 8.62 (median cycle, 9; SE, 2.1). These data indicate that patients who developed severe PCNV early in their course of treatment (before cycle 4) were more likely to eventually develop AV, compared to patients who developed severe PCNV later in their therapy ($P < 0.01$).

Twenty-one of 22 patients who experienced severe PCNV had one or more 50% reductions in prescribed CMF dose. One patient discontinued CMF therapy after

TABLE 2.—PCNV and CMF dose

Group	No. (%) of patients			
	Total	No PCNV	Moderate PCNV	Severe PCNV
Standard-dose CMF	23	1 (4)	4 (17)	18 (78)
Low-dose CMF	29	5 (17)	20 (69)	4 (14)*
Total	52	6 (12)	24 (46)	22 (42)

*$P < 0.001$.

TABLE 3.—AV and PCNV severity

Group	No. (%) of patients			
	Total	No PCNV	Moderate PCNV	Severe PCNV
With AV	17	0	4 (23.5)	13 (76.5)
Without AV	34	6 (17.6)	20 (58.8)	8 (23.5)*
Total	51†	6 (11.8)	24 (47.1)	21 (41.2)

*$P < 0.001$.

†1 patient who refused treatment because of severe PCNV after cycle 1, Day 1, could not be categorized as having or not having AV.

cycle 1, Day 1, and thus is not recorded as having a dose reduction. Of the 21 women who received protocol dose reductions, 17 (81%) were receiving standard-dose CMF, while only four (19%) were receiving low-dose therapy. Fourteen of 52 patients (27%) discontinued CMF adjuvant chemotherapy before cycle 24; ten of the 14 (71%) who discontinued therapy cited nausea and vomiting as the major reason for stopping treatment. All ten patients who discontinued therapy because of nausea and vomiting had experienced severe PCNV: seven (70%) had received standard-dose CMF and three (30%) had received low-dose CMF. Seven of the ten women (70%) who discontinued CMF adjuvant chemotherapy due to nausea and vomiting had experienced AV. Four of 14 women who discontinued therapy did so for reasons unrelated to nausea and vomiting.

DISCUSSION

In this study of 52 women randomized between two regimens of CMF adjuvant chemotherapy for stage II or III breast carcinoma, 17 (33%) developed AV. AV occurred more frequently in patients with severe PCNV and in patients receiving the higher dose of CMF. Ten of 14 women who discontinued treatment did so because of nausea and vomiting and seven of these ten had experienced AV.

Since patients in the community cancer network were not included in our chart review, the AV incidence of 33% in the JHOC population may not accurately reflect the incidence in the larger group. The retrospective nature of this study limited the observed rate of AV to that recorded by the health care provider, which in turn limits the accurate assessment of the incidence of AV. On the other hand, the reliability and validity of the retrospectively derived incidence figure may be enhanced by the fact that two thirds of the sample population were followed by one clinician (P. M. Wilcox). These data should not be generalized to larger populations without further study, because the incidence of AV may differ for patients with breast cancer treated with similar regimens in different settings or treated with different regimens.

There was a significant relationship between both higher doses of CMF adjuvant chemotherapy and severe PCNV and the development of AV. Since no patient developed AV without first developing PCNV, it seems likely that the relationship between the higher dose of CMF and AV is mediated through the severe PCNV caused by that regimen. The data regarding the time of onset of PCNV show that, while all patients who developed mild PCNV did so at approximately the same time, women who developed severe PCNV before cycle 4 were at a significantly greater risk for developing AV.

The pathogenesis of AV is unknown. However, since AV did not develop in any woman who did not first have at least moderate PCNV, AV may be a Pavlovian conditioned response (7,8). Reports in the literature suggest that systematic desensitization and relaxation techniques have been helpful for some patients with AV (9,10). Since AV and severe PCNV resulted in the reduction of CMF doses and accounted for 71% of the treatment dropouts, these syndromes may indirectly affect disease-free interval and survival. Bonadonna and Valagussa (11) have suggested that the length of the disease-free interval and survival are related to the total dose of CMF administered.

In our population, AV and PCNV were significant problems that warrant better understanding and more effective interventions. Studies that prospectively assess nausea and vomiting syndromes are indicated, as are studies that use the expertise of multidisciplinary investigators in planning, implementing, and evaluating interventions for amelioration and/or prevention of AV and PCNV.

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Combined Doxorubicin and Radiation Therapy in Malignant Pleural Mesothelioma[1,2]

Clive Sinoff, Geoffrey Falkson,* A. G. Sandison, G. De Mûelenaere [3]

Ten patients with histologically confirmed inoperable malignant mesothelioma of the pleura were treated with doxorubicin and fractionated radiotherapy courses. Three patients derived significant clinical benefit from this treatment, although only one of the three had measurable tumor shrinkage that could be defined as partial response. Two of the ten patients showed only progressive disease, while the remaining five showed disease stabilization for 30–100 weeks. The treatment was subjectively well-tolerated and hematopoietic toxicity was acceptable. Radiation pneumonitis did not occur. Two of the four patients who lived ≥ 94 weeks developed fibrosis of the irradiated hemithorax. The median survival time for all patients was 46 weeks. Although the combined treatment could be given with acceptable toxic effects and although four patients benefited from it, the best objective assessment, namely, survival time, did not appear to be adequately influenced to justify an extension of this series. [Cancer Treat Rep 66:1605–1607, 1982]

Long-term survival of patients with malignant mesothelioma after radiation therapy alone has been reported in isolated instances (1,2), but the usual result is disappointing (1–3). The best results reported in the treatment of this disease have been with the combined use of procarbazine and radiation therapy (3). In that study, various irradiation schedules were used. The best response was observed among 11 patients receiving 1800–2000 rad in 2 weeks and in 12 patients treated with < 1600 rad; both treatments were repeated every 2 months. The total dose of radiation is difficult to interpret because up to eight courses of treatment were given in up to 2 years.

Doxorubicin as a single agent showed promising activity in early studies (4,5). In an Eastern Cooperative Oncology Group (ECOG) study of 51 patients, doxorubicin showed no important activity (6). The present study was undertaken to assess whether it is possible to use the multiple fractionated irradiation technique developed in Pretoria (3,7–10) together with full therapeutic doses of doxorubicin, without causing unacceptable toxicity. It was hoped that the therapeutic benefit that might be obtained from doxorubicin could be enhanced by the addition of radiation therapy. The advantage of irradiation fractionation is that a large dose of radiation would not be given to nonresponders, and responders could be carefully monitored while the cumulative dose of radiation increased.

MATERIALS AND METHODS

Six men and four women ranging in age from 34 to 69 years (median, 56) with advanced mesothelioma confined to one hemithorax were treated during 1979 and 1980. All patients had inoperable, histologically confirmed malignant pleural mesothelioma. The ECOG performance status (PS)[4] was 3 in one patient, 2 in two patients, 1 in six patients, and 0 in the remaining patient. Thoracotomy was performed in all ten patients. Resection was attemped in one patient without success. In the remaining nine patients, disease was too advanced to permit resection, although resection had been considered in all patients. An estimate of the degree of pleural involvement (from fine nodulation to massive tumor in the hemithorax) obtained at thoracotomy was combined with the radiologic findings to assess the tumor load in each patient.

It was not possible to estimate all areas of pleural thickening in the presence of massive pleural effusion. Patients were evaluated following thoracocentesis (table 1). Extent of disease was defined as follows: *moderate*—loss of < 1/3 of radiographically visible lung tissue (extent I); *marked*—loss of 1/3–2/3 of radiographically visible lung tissue (extent II); and *extensive*—loss of 2/3 of radiographically visible lung tissue (extent III). This classification was used irrespective of whether the lung was compressed by tumor, infiltrated by tumor, or considered

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[2]Supported in part by a grant from the National Cancer Association of South Africa.
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[4]ECOG PS criteria: 0 = normal activity; 1 = symptoms but ambulatory; 2 = in bed < 50% of time; 3 = in bed > 50% of time; and 4 = 100% bedridden.
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TABLE 1.—Doxorubicin and radiotherapy in treatment of malignant pleural mesothelioma

Patient No.	Age (yrs)*	Sex	PS†	Extent of disease†	Time to treatment failure (wks)*	Survival (wks)*	Comments
1	37	M	0	II	32	44	Reduction of pleural thickening (> 50%); clearing of pleural effusion; and weight gain
2	49	F	1	I	100	106	Fibrosis of irradiated hemithorax; improvement in PS; and reduction in thoracic pain
3	69	F	2	II	82	96	Fibrosis of irradiated hemithorax; improvement in PS; reduction in chest pain and dyspnea
4	34	F	2	III	32	45	Improvement in PS; and reduction in pleural pain, dyspnea, and cough
5	56	F	1	II	90	94	No change
6	64	M	1	I	52	108	No change
7	44	M	1	III	30	48	No change
8	68	M	1	II	30	44	No change
9	56	M	3	II	13	28	Disease progression only
10	69	M	1	II	9	19	Disease progression only

*Median age, 56 yrs; median survival, 46 wks ($10^1/_2$ mos); median time to treatment failure, 32 wks.
†*See* text for definitions.

to contain metastatic mesothelioma within the lung tissue. A separate estimation for pericardial involvement was not possible, although the pericardium was considered to be involved in all ten patients. None of the patients had received chemotherapy or radiotherapy prior to entry in this study. All patients were directly referred from thoracic surgery. Renal, hepatic, and cardiac functions were normal. Because of the difficulties in objectively evaluating response in patients with malignant pleural mesothelioma, survival was the primary end point for evaluation in this study. Response was measured clinically, with emphasis on respiratory reserve, and radiologically. Special attention was paid to change in PS and to subjective change.

Doxorubicin was given at a dose of 60 mg/m^2 iv every 3 weeks. The dose was decreased by 50% if the wbc count on Day 1 of each treatment cycle was < 4000 but > 3000/mm^3 and/or the platelet count was < 100,000 but > 75,000/mm^3. The cycle was postponed until recovery when the wbc count was < 3000/mm^3 and the platelet count was < 75,000/mm^3. The maximum cumulative dose of doxorubicin allowed was 500 mg/m^2.

Radiotherapy was given concomitantly with the first, third, fifth, and seventh doses of doxorubicin. Cobalt-60 radiation was used, giving a tumor dose of 200 rad/day, to a total dose of 1000 rad in 5 days, commencing on Monday and ending on Friday. Parallel opposing fields to include the involved side of the hemithorax plus one half of the mediastinum were used. The field size varied from 19 × 19 cm to 25.5 × 27 cm. No correction was made for lung tissue. A maximum of four such courses of radiotherapy was planned for each patient.

RESULTS

Seven of the ten patients received the planned maximum treatment (four courses of radiotherapy and a cumulative doxorubicin dose of 500 mg/m^2). Three patients received less than the planned maximum dose because of disease progression. One patient received the full four courses of irradiation but only 530 mg of doxorubicin, one received three courses of radiation therapy and 400 mg of doxorubicin, and one received only one course of irradiation but 340 mg of doxorubicin.

Toxicity

Leukopenia < 4000 but > 3000 cells/mm^3 was documented in four patients. Leukopenia < 3000 but > 2000 cells/mm^3 was documented in three patients. No patient had a wbc count < 2000/mm^3. The seven patients with mild or moderate leukopenia required dose modification (reduction in dose or postponement). Thrombocytopenia requiring dose modification did not occur. Nausea and vomiting occurred in six patients but was never severe. One patient developed cardiac failure 14 months after completion of therapy. This was a preterminal event but was possibly related to treatment; it occurred $93^1/_2$ weeks after the start of treatment. Two patients who received the full planned dose of radiation and doxorubicin developed total fibrosis of the irradiated hemithorax. This was the expected reaction to the irradiation. None of the patients had acute radiation pneumonitis or esophagitis.

Response

One patient had a partial response as judged by a definite reduction in pleural thickening (> 50%) and pleural fluid. This patient's PS remained 0, and no new lesions developed during the 32 weeks before disease progression occurred.

Two female patients, both of whom developed fibrosis of the irradiated hemithorax, were considered to be objectively improved and had marked subjective improvement. They had a decrease in respiratory distress with definite subjective improvement, showed improvement in PS, and were able to return to work. These patients survived 106 and 96 weeks. Neither patient had total involvement of the hemithorax at the start of treatment, as judged by the above criteria. It was not possible to distinguish clinically between fibrosis and tumor. Neither patient showed disease progression or extension. Another patient had subjective improvement in PS, and the tumor remained static for 8 months.

Four patients had no change in tumor status for 90, 52, 30, and 30 weeks. In these patients the PS and subjective state remained constant. The remaining two patients showed measurable disease progression despite treatment.

The time to treatment failure varied from 9 to 100 weeks (median, 32). Survival ranged from 19 weeks ($4^1/_2$ months) to 108 weeks (26 months), with a median of 46 weeks ($10^1/_2$ months).

DISCUSSION

The combined treatment was well-tolerated. Only one of the ten patients developed overt cardiac failure and this occurred at a time when the patient had progresssive disease. Hematologic and gastrointestinal toxic effects were acceptable. The absence of symptomatic pneumonitis is most probably due to the prolonged time span ($4^1/_2$ months) over which the irradiation was administered. Such fractionation has far less biologic effect than the same dose given consecutively in a compressed time span. The incidence of symptomatic pneumonitis in patients receiving one 800-rad prophylactic lung radiation treatment for osteogenic sarcoma is low. With a dose of 1000 rad over 5 days, symptomatic pneumonitis would not be expected if irradiation had been the only treatment. The total dose of doxorubicin ranged from 340 to 800 mg, with a median of 615 mg over 22 weeks. This is considered to be an adequate dose of doxorubicin. It is improbable that a higher dose of radiation would be tolerated.

Partial response as documented by strict tumor measurement occurred in only one patient, but an objective improvement occurred in another two patients. The disease progressed relentlessly in only two patients.

Survival ranged from 19 to 108 weeks (median, 46; $10^1/_2$ months). This is comparable to the results of Chahinian and Holland (11) using doxorubicin and nonfractionated irradiation. Similar survival times have been reported in patients with pleural mesothelioma treated with a variety of single agents or combinations of agents or radiation therapy alone (12–17). Because the major measurable end point of the present study is survival, the most likely explanation for the lack of benefit is that neither doxorubicin nor radiotherapy alone is sufficiently effective in the treatment of this disease to make the combined modality approach worthwhile. The treatment combination was relatively well-tolerated; however, this is not sufficient motivation to extend the study.

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Upper Hemibody and Local Chest Irradiation as Consolidation Following Response to High-Dose Induction Chemotherapy for Small Cell Bronchogenic Carcinoma—A Pilot Study[1,2]

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Encouraging results of the combination of upper hemibody irradiation (UHBI) and local chest irradiation (LCI) combined with standard-dose chemotherapy in patients with extensive small cell bronchogenic carcinoma led us to a second pilot study utilizing the same radiation program combined with high-dose induction chemotherapy. Fourteen patients with small cell bronchogenic carcinoma, five with extensive disease and nine with localized disease, were treated with cyclophosphamide (1.5 g/m² iv, Days 1 and 22), lomustine (70 mg/m² orally, Day 1), and methotrexate (15 mg/m² twice weekly during Weeks 2, 3, 5, and 6). UHBI (600 rads) was given during Week 6 in a single dose and LCI was given during Week 7 (2000 rads/five fractions) to the tumor and mediastinum. Maintenance chemotherapy began in Week 12 with cyclophosphamide (700 mg/m² iv every 3 weeks) and lomustine (70 mg/m² orally every 6 weeks). Twelve patients were evaluable for response and toxicity (eight with limited disease). There were three complete responses and seven partial responses after induction chemotherapy. After completion of the consolidation radiation therapy, all 12 patients had a response: six complete responses and six partial responses. Acute toxic effects included nausea and vomiting in eight patients, fever in five, and hypotension and angina in one. Subacute toxic effects included nausea, vomiting, and dehydration in two patients who required hospitalization, prolonged aplasia in one, and reversible radiation esophagitis in three. Three patients had radiation pneumonitis including one with bilateral diffuse disease that led to death from respiratory failure. Only two of 12 patients received their maintenance therapy on schedule. Treatment failures occurred within the LCI field in seven patients and in distant metastatic sites in six. The median time to first relapse was 7 months and the median survival was 9 months. Because of toxicity, treatment delays, and poor survival in this group of patients, we cannot recommend this combined modality approach. [Cancer Treat Rep 66:1609–1612, 1982]

Progress in the treatment of small cell bronchogenic carcinoma (SCBC) has reached a plateau (1–3). Aggressive combination chemotherapy programs have resulted in high response rates and in an increased percent of complete remissions. Survival of all patients has increased about fourfold to fivefold, with the median survival times increasing from 2.5 to about 12 months with modern therapy (1,2). However, despite the initial responsiveness of their tumors to chemotherapy, patients with disease remission have a pattern of continuous relapse and ultimately die of progressive disease. Innovative efforts to prevent relapses in general or in specific sites, particularly in complete responders, have included consolidative chest irradiation in patients with limited disease (1), prophylactic brain irradiation (4), cyclic alternating non-cross-resistant combination chemotherapy programs (5), intensive high-dose chemotherapy (3), and the addition of thymosin fraction V (6). None of these approaches has resulted in unqualified success in solving the problem of continuous relapse.

Recently, a pilot study was performed of upper hemibody irradiation (UHBI) and local chest irradiation (LCI) combined with standard doses of cyclophosphamide and lomustine in patients with extensive SCBC (7). The UHBI was intended as a form of systemic therapy that could substitute for a cycle of chemotherapy and possibly consolidate the treatment of disease in the primary and major metastatic sites (mediastinum, liver, upper abdominal

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lymph nodes, adrenals, bones, and brain). The toxicity of this combined modality approach was acceptable, and the response rate and median survival were almost identical to those of an historical control group that had received chemotherapy alone. The encouraging results of this feasibility study led us to a second pilot study utilizing the same radiation program combined with high-dose induction chemotherapy.

MATERIALS AND METHODS

Fourteen patients with SCBC were entered in this combined modality study. Five patients had extensive disease and nine had localized chest disease. The median performance status (PS) was 1 and the mean PS was 1.2 (Eastern Cooperative Oncology Group PS 0–4). Two patients (one with extensive and one with localized disease) did not receive the consolidative radiation therapy program: the patient with local disease died of sepsis resulting from leukopenia during high-dose induction chemotherapy and the other patient with a low PS after the induction chemotherapy was not eligible for the UHBI. The remaining 12 patients who received the entire induction treatment program were evaluable for toxic effects and response. Their median age was 60 years (oldest patient, 69 years old). All patients had adequate peripheral blood determinations (hemoglobin > 10 g/100 ml, wbc count > 4000/mm^3, and platelet count > 100,000/mm^3), renal function (BUN < 20 mg/100 ml), and hepatic function (bilirubin less than two times normal).

Induction chemotherapy consisted of cyclophosphamide (1.5 g/m^2 iv on Days 1 and 22), lomustine (70 mg/m^2 orally on Day 1), and methotrexate (15 mg/m^2 orally twice weekly during Weeks 2, 3, 5, and 6). There was no dose modification for cytopenias during the 6-week induction period. Patients were treated with consolidation therapy between the 7th and 9th weeks. Maintenance chemotherapy was scheduled to begin in Week 12 with cyclophosphamide (700 mg/m^2 iv every 3 weeks) and lomustine (70 mg/m^2 orally every 6 weeks) until tumor progression.

Consolidation radiation therapy consisted of UHBI and LCI. The UHBI was delivered as a single dose of 600 rads to the midthickness of the patient above the iliac crest at a rate of 30–40 rads/minute. The technique of irradiation and the premedication program to ameliorate nausea and avoid hypotensive episodes have been published previously (8). One week later, LCI was administered with anterior and posterior portals that were designed to encompass the primary tumor, the mediastinum, and both supraclavicular areas. A posterior spinal cord block was added at 1200 rads to the involved fields to limit the radiation dose to the spinal cord. Thus, the central mediastinal structures received a reduced radiation dose as well. In those patients with disseminated disease involving bone, local radiation therapy (2000 rads in divided fractions) was administered concurrent with the local chest irradiation. The total local dose of 2000 rads was delivered in five fractions of 400 rads each over a period of 1 week.

All patients were followed until their deaths. Responses to and toxic effects of the therapy, as well as the delays in therapy and sites of relapse, were recorded and analyzed. Eastern Cooperative Oncology Group standard criteria for defining response and toxicity were utilized. Limited disease was defined as disease of one hemithorax including the mediastinum but not ipsilateral supraclavicular nodes; extensive disease was defined as disease more advanced than limited disease.

RESULTS

Ten of the 12 evaluable patients responded to the induction chemotherapy: three complete responses (CRs) in patients with limited disease, and seven partial responses (PRs) (three in patients with limited and four in patients with extensive disease).Two patients with limited disease had minor responses to the induction chemotherapy. After completion of the consolidation radiation therapy, all patients achieved a response: six CRs and six PRs. Three patients with a PR after chemotherapy (two with limited and one with extensive disease) converted to CR status and both chemotherapy nonresponders achieved PRs.

As expected, the intensive chemotherapy regimen, which was not modified for blood cell counts during the 6 weeks of induction, was toxic. All patients experienced some degree of pancytopenia although severe leukopenia was usually of short duration. Ten patients developed wbc count nadirs < 1000/mm^3; nadirs for the two remaining patients were 2900 and 3400/mm^3. Seven patients developed platelet count nadirs between 20,000 and 50,000/mm^3, and another had a nadir of 77,000/mm^3. Five of the original 14 patients experienced fever and leukopenia, including one who had salmonellosis, one who had a renal stone and urinary sepsis with *Proteus* organisms, two who required hospitalization for empiric antibiotics, and one who died from sepsis. One patient required platelet transfusions during an episode of thrombocytopenia and occult gastrointestinal blood loss. Five patients experienced mucositis from the methotrexate which was mild and quickly reversible. One patient had hemorrhagic cystitis from his first dose of cyclophosphamide, but recovered completely and received subsequent courses of cyclophosphamide with careful iv hydration.

Acute toxicity of the UHBI included nausea and vomiting in eight patients which began abruptly at the conclusion of the UHBI and was self-limited, and fever between 101°F and 104°F in five patients the night of the UHBI treatment. One patient developed intractable nausea and vomiting and required readmission for iv fluids and sup-

portive care. A final patient with underlying symptomatic coronary artery disease developed severe chest pain and mild hypotension during and immediately following UHBI and required admission to the coronary care unit for preinfarction angina. She recovered completely from this acute episode, but subsequent chronic malaise prevented initiation of maintenance chemotherapy.

Subacute toxic effects resulting from the UHBI plus the LCI (and presumably the substrate of high-dose chemotherapy that preceded the radiation) were observed in nine of 12 patients. Five patients required rehospitalization either during or immediately following the LCI: two had intractable nausea and vomiting; one developed prolonged aplasia; one developed acute fever, malaise, anorexia, weight loss, and leukopenia; and one developed fever, anorexia, pulmonary infiltrates, and hypoxemia. Three patients had self-limited radiation esophagitis; one patient had otitis media. All patients with subacute toxic effects recovered completely, except for the patient who developed prolonged pancytopenia. This patient received UHBI 1 week late due to a wbc count of 2700/mm^3. Following the completion of UHBI and LCI, the wbc and platelet counts ranged between 2000 and 3000 and 30,000 and 80,000/mm^3, respectively, for the next 7 months until her disease recurred.

Late toxic effects from this combined modality induction program were experienced by four patients, including the one patient with pancytopenia (which precluded subsequent maintenance chemotherapy), two patients with localized radiation pneumonitis (both improved with corticosteroid therapy), and one patient with irreversible diffuse bilateral radiation pneumonitis while in clinical CR. This latter patient underwent open-lung biopsy to confirm the diagnosis and eventually died from respiratory failure with a chest X-ray showing diffuse interstitial disease.

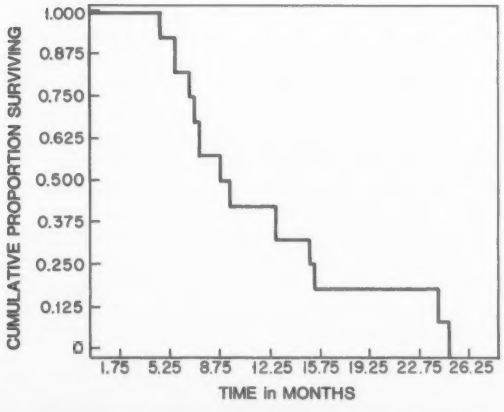

FIGURE 1.—Actuarial survival curve for all evaluable patients.

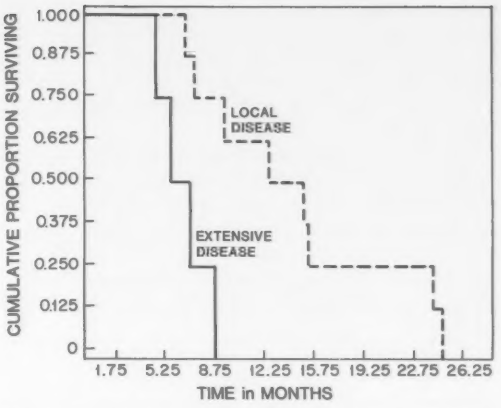

FIGURE 2.—Actuarial survival curves for extensive-disease patients compared to limited-disease patients.

Only two of 12 patients were able to receive maintenance chemotherapy without delay as well as in full dose. One of these patients died a respiratory death with bilateral radiation pneumonitis after three doses of maintenance chemotherapy; the other developed a brain metastasis after two cycles of chemotherapy and died 1 month later. Three patients never received maintenance chemotherapy because of chronic pancytopenia (one patient), severe unresolved malaise from induction therapy (one), and early progressive disease (one). The remaining seven patients either had delays in initiating maintenance followed by full doses (one patient) or attenuated doses (five patients) or had no delay in initiation of maintenance followed by dose reductions (one patient). Dose reductions ranged between 50% and 75% for either leukopenia or thrombocytopenia or both. Delays ranged between 1 and 2 weeks.

Seven patients relapsed first within the local radiation field, six relapsed at distant sites (two relapsed simultaneously in the chest and distantly), and one died a respiratory death before relapse. In three of the seven local recurrences, inadequate coverage by the local radiation fields may have accounted for the local failures. The median time to first relapse was 7 months (range, 3–14.5) and median survival of all patients was 9 months (range, 5–25) (fig 1). For the eight patients with initially limited disease, the median time to first relapse was 8 months and the median survival was 12 months (fig 2).

DISCUSSION

Half-body irradiation has been suggested as an innovative form of consolidation therapy in the treatment of SCBC (1,2,7,9). This form of "systemic irradiation" offers a 1–3-log cell kill that may substitute for a cycle of sys-

temic chemotherapy (1). Concerns about its use include (*a*) the enhanced toxicity of combined aggressive chemotherapy and irradiation (7), (*b*) the danger of radiation pneumonitis, both acute and chronic (10), and (*c*) the risk of treatment delays that might undermine the control of systemic disease.

This pilot study reinforces some of the above concerns. As participants in the first pilot study utilizing lower doses of chemotherapy (7), we were already concerned about treatment delays and attenuation of maintenance therapy. However, in that study, toxicity was acceptable. In this study, combining higher doses of induction chemotherapy with UHBI and LCI resulted in unacceptable toxicity.

The toxicity of the radiation therapy program that immediately followed aggressive chemotherapy was high. Five patients required early rehospitalization, including one who developed chronic marrow hypoplasia and two who were quite ill and required prolonged hospital stays. Three patients with underlying chronic obstructive pulmonary disease developed radiation pneumonitis, one of whom died of diffuse interstitial pneumonitis and respiratory failure induced by the UHBI.

Delays in maintenance chemotherapy and dose reductions were necessary in most patients. No patient in this study received full-dose maintenance chemotherapy on schedule for > 6 weeks.

Finally, and most disappointingly, despite the good PS of this group of patients, the high proportion of patients with limited disease (67%), and their initial excellent response rate (100% CR + PR for evaluable patients, with 50% CR), the survival results were poor. Seven patients relapsed locally within the first year, and the median time to relapse and median survival times were relatively short. Even analyzing the best subgroup (those with limited disease) did not show a significant benefit to this therapy. Distant failures occurred early in many patients within the UHBI portal: brain, liver, adrenals, and pleura.

Though more extensive local radiation portals and higher mediastinal X-ray doses may have decreased the high incidence of local failure, it would not have improved the pattern of complications seen and may have increased them. Thus, because of toxic effects, treatment delays, and poor survival in this predominantly favorable group of patients with SCBC, we cannot recommend this combined modality approach in patients with SCBC.

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Phase I–II Study of the Combination of 5-FU, Doxorubicin, Mitomycin, and Semustine (FAMMe) in the Treatment of Adenocarcinoma of the Stomach, Gastroesophageal Junction, and Pancreas[1]

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One hundred and fifteen patients with advanced gastrointestinal cancer (stomach cancer, 42 patients; gastroesophageal junction cancer, ten; pancreatic cancer, 32; and other upper gastrointestinal cancers, 31) were treated with a combination chemotherapy regimen consisting of 5-FU, doxorubicin, mitomycin, and semustine (methyl-CCNU) (FAMMe). Of the 31 patients with stomach cancer who were evaluable for response and had had no previous chemotherapy, 12 (39%) achieved complete or partial remission. One of eight (12%) patients with gastroesophageal junction cancer and five of 23 (22%) patients with pancreatic cancer achieved a partial remission. The median duration of survival for all patients with adenocarcinoma of the stomach was 7.1 months. The median duration of survival for responding patients with stomach cancer was 13.6 months, and the median survival for nonresponding patients was 6.1 months. FAMMe chemotherapy was generally well-tolerated and can be administered in adequate doses without producing prohibitive myelosuppression. The starting dose should be reduced for patients ≥ 70 years old or for patients who have received pelvic or vertebral radiation therapy. FAMMe is effective against advanced gastric cancer; however, because this was not a randomized comparative study of the relative effectiveness of FAMMe and FAM (5-FU, doxorubicin, and mitomycin), no recommendation for the use of one regimen instead of the other for advanced adenocarcinoma of the stomach can be made. FAMMe chemotherapy cannot be recommended for advanced adenocarcinoma of the pancreas and gastroesophageal junction.
[Cancer Treat Rep 66:1613–1617, 1982]

Patients with adenocarcinoma of the stomach, gastroesophageal junction, or pancreas have a dismal prognosis. For all patients, the 5-year survival rate ranges from 10% for stomach cancer to < 1% for pancreatic cancer (1–3). For patients who undergo "curative" resection, the 5-year survival rate ranges from 20% for stomach cancer to < 5% for pancreatic cancer (1–3). Because most tumors are unresectable at the time of diagnosis and most resected cancers recur, effective chemotherapy regimens for the palliation of symptoms and prolongation of survival are needed.

Combination chemotherapy regimens using drugs active against gastric and pancreatic cancers have improved response rates when compared with those from single-agent chemotherapy (4–12). Combination chemotherapy offers improved survival for advanced gastric cancer (4) but not for pancreatic cancer (5,6,10,11). Most regimens are based on 5-FU plus one or more of the following drugs: a nitrosourea, doxorubicin, and mitomycin (4–12). The results of therapy with a four-drug regimen for advanced gastric cancer containing 5-FU, doxorubicin, mitomycin, and semustine (methyl-CCNU) (FAMMe), given over an 8-week cycle, were reported (13). The 11% objective response rate was worse than the response rate achieved with most other multidrug regimens, and the median survival was similar to the median survival reported for most other multidrug regimens (4–12). This disappointing finding might be the result of drug dose and scheduling.

Our study was designed to use a regimen with the same four drugs at different doses and a different schedule. The aims of our phase I–II study were to determine the maximum tolerable dose for the FAMMe combination chemotherapy regimen and to assess the efficacy of this regimen for treatment of advanced adenocarcinoma of the stomach, gastroesophageal junction, and pancreas.

PATIENTS AND METHODS

One hundred and fifteen patients with histologic confirmation of advanced upper gastrointestinal cancer were

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entered in the study between January 1979 and January 1981. Of these, 42 had adenocarcinoma of the stomach, ten had adenocarcinoma of the gastroesophageal junction, and 32 had adenocarcinoma of the pancreas. Adenocarcinoma of the gastroesophageal junction was considered to be a different disease than adenocarcinoma of the stomach (14,15). The remaining 31 patients had various other upper gastrointestinal cancers: eight patients, hepatocellular carcinoma; six, intestinal carcinoid; four, gallbladder; five, bile duct; two, ampulla of Vater; three, adenocarcinoma of the small intestine; two, pancreatic islet cell; and one, pancreatic acinar. The characteristics of the patients with adenocarcinoma of the stomach, gastroesophageal junction, or pancreas are shown in table 1. All patients gave written, informed consent prior to treatment, in accordance with institutional policy.

The dose and schedule for the FAMMe regimen are illustrated in table 2. During the phase I study, patients were entered at sequential starting doses. When the maximum tolerable dose was determined to be dose level C, most other patients were started at that level. Patients at high risk of hematologic toxicity, defined as being ≥ 70 years old, having had previous vertebral or pelvic radiation therapy, or having had prior therapy with alkylating agents, often started at dose level B. Dose modification for subsequent cycles was based on the wbc or neutrophil and platelet count nadirs during the preceding cycle. The dose of doxorubicin was reduced if liver function was impaired (table 1).

Because this was a phase I–II study, measurable lesions were not required; however, most patients entered were evaluable for response (table 1). Objective response was determined by physical examination, roentgenograms, radionuclide scans, computerized tomograms, ultrasonograms, and endoscopy. When radionuclide liver scans were used to quantitate response to chemotherapy, discrete areas seen on two views, single or multiple, > 2 cm in diameter with > 50% decrease in count rate were required. When endoscopy was used, indicator lesions were measured in reference to an open biopsy forceps. Measurement of response using these diagnostic modalities was performed by the consultants who performed the diagnostic study and also by one of the study investigators. A complete response was defined as no objective signs of residual cancer. A partial response was defined as a reduction of ≥ 50% in the product of the longest perpendicular diameters of the best measurable lesion; it was defined for liver metastasis as a reduction

TABLE 1.—Patient characteristics

Characteristic	No. of patients		
	Gastroesophageal junction adenocarcinoma	Stomach adenocarcinoma	Pancreatic adenocarcinoma
Entered	10	42	32
Nonevaluable	2	7	9
Evaluable for response	8	35	23
Mean age in yrs	55	57	59
Sex			
Male	7	21	13
Female	1	14	10
Metastasis			
Local	7	32	23
Liver	3	19	11
Lung	4	8	2
Abdomen	1	17	10
Bone	1	2	1
Nodes	2	4	3
Skin	1	2	1
Prior therapy			
Radiation therapy to tumor	3	2	1
Radiation therapy to pelvis or vertebrae	2	2	3
Chemotherapy	0	4	0
Performance status*			
0	1	13	5
1	3	11	6
2	1	10	4
3	3	1	8
4	0	0	0

*Eastern Cooperative Oncology Group criteria.

TABLE 2.—Schema for FAMMe regimen dose, schedule, and toxicity adjustments

a. Dose and schedule

Drug, route	Dose (mg/m^2)				Day				
	A	B	C	D	1*	8†	29*	36†	57(1)*
5-FU, iv	300	450	600	750	X	X	X	X	X
Doxorubicin, iv	15	22.5	30	37.5	X	—	X	—	X
Mitomycin, iv	5	7.5	10	10	X	—	—	—	X
MeCCNU, orally	50	75	100	125	X	—	—	—	X

b. Toxicity adjustments

All 4 drugs reduced for myelosuppression nadir				Doxorubicin only reduced for liver function		
Polymorphonuclear count ($cells/mm^3$)	or	Platelet count ($cells/mm^3$)	% dose reduction	Bilirubin (mg/100 ml)	or	SGOT (× normal)
750–1000	or	50,000–75,000	25	—		SGOT 2–3×
< 750	or	< 50,000	50	1.2–3		SGOT > 3×
—		—	75	> 3		—

*Minimum wbc count of $3500/mm^3$ and platelet count of $100,000/mm^3$ to start.
†Minimum wbc count of $2500/mm^3$ and platelet count of $75,000/mm^3$ to start.

of ⩾ 30% in the sum of the subcostal and subxyphoid measurements. In addition, a partial response required that there be no increase in any lesion and no new metastasis. Stable disease was defined as either no change or no regression or a < 25% increase in any lesion, and no new metastasis. Disease progression was defined as a ⩾ 25% increase in any lesion, or a new metastasis. To qualify as a response or stable disease the response or initial status had to be maintained for at least 8 weeks.

Survival and duration of response were determined from the start of therapy. Survival data were calculated by the Kaplan and Meier method (16) and statistically evaluated by the Gehan modification of the generalized Wilcoxon test (17). Chi-square statistical analysis was used to evaluate the possible relationship between the patient characteristics (table 1) and response to chemotherapy and survival. For four patients with adenocarcinoma of the stomach, Fisher's exact test for independence was used to evaluate the effect of the prior chemotherapy on subsequent response rates.

RESULTS

Objective Response

Twelve of 35 patients (34%) with adenocarcinoma of the stomach achieved a complete or partial response (table 3). The median duration of response was 6 months (range, 2–8). The median duration of survival for all patients with adenocarcinoma of the stomach was 7.1 months. The median duration of survival for responding and nonresponding patients was 13.6 and 6.1 months, respectively ($P < 0.006$).

Five of 23 patients (22%) with adenocarcinoma of the pancreas achieved a partial response (table 3). The median duration of response was 6 months (range, 2–8). The median duration of survival for all patients with adenocarcinoma of the pancreas was 7.4 months. The difference in the median survival time between responding and nonresponding patients was not statistically significant ($P = 0.48$).

One of eight patients (12%) with adenocarcinoma of the gastroesophageal junction achieved a partial remission (table 3) lasting 6 months. Twenty-one of the 31 patients with various other gastrointestinal cancers were evaluable for response. The partial response rates for these cancers were: $33^1/_3$% (two of six patients), hepatocellular carcinoma; 60% (three of five), intestinal carcinoid; 0 (none of three), gallbladder; 100% (one of one), bile duct; 0 (none of one), ampulla of Vater; 50% (one of two), adenocarcinoma of the small intestine; 50% (one of two), pancreatic islet; and 0 (none of one), pancreatic acinar.

Patient characteristics that potentially influenced response were analyzed (table 1). Sex, age, physical performance status, unresectable primary cancer, and sites of metastasis did not affect response rates for patients with adenocarcinomas of the stomach, gastroesophageal junction, and pancreas (χ^2). Radiation therapy to the unresected primary tumor had no effect on subsequent response rates for adenocarcinomas of the stomach, gastroesophageal junction, and pancreas (χ^2). None of the patients with adenocarcinoma of the gastroesophageal junction or pancreas received chemotherapy prior to entering this study. Four patients with adenocarcinoma of the stomach received prior chemotherapy. All four patients were nonresponders. For these four patients the effect on subsequent response rates was statistically significant (Fisher's exact test for independence). If these

TABLE 3.—Objective response

Response	No. of patients (%)		
	Gastroesophageal junction adenocarcinoma	Stomach adenocarcinoma	Pancreatic adenocarcinoma
Complete	0	1 (3)	0
Partial	1 (12)	11 (31)	5 (22)
Stable	2	11	11
Disease progression	5	12	7
Total	8	35	23

four nonresponders who had received prior chemotherapy are removed from the calculation of response rate, the complete plus partial response rate for stomach cancer is 39%.

Toxicity

The dose-limiting toxic effect was myelosuppression. Seventy-six percent of the 115 patients started at dose level C, 21% at level B, and 3% at level A. Subsequent dose adjustments were almost always downward, indicating the cumulative myelosuppression of this four-drug regimen. By the fourth chemotherapy cycle, 5% of the 19 remaining patients were treated with dose level D, 21% at level C, 32% at level B, and 42% at level A. Only one patient received nine cycles of chemotherapy.

There were two wbc count nadirs, between Days 20 and 26 and Days 38 and 43, and two platelet count nadirs, between Days 19 and 24 and Days 31 and 50. Severe myelosuppression was defined as a wbc count nadir $\leq 1000/mm^3$, a neutrophil count nadir $\leq 500/mm^3$, or a platelet count nadir $\leq 25,000/mm^3$. Adequate data were available to evaluate 186 chemotherapy cycles for myelosuppression. Thirteen percent of these cycles were characterized by severe myelosuppression. There were two deaths related to severe myelosuppression. One of the patients had received radiation therapy to a significant volume of bone marrow prior to chemotherapy and both were $\geq$ 70 years old. Two pretreatment factors appeared to increase the risk of severe myelosuppression: age $\geq$ 70 years and radiation therapy.

DISCUSSION

The FAMMe regimen was generally well-tolerated. Although the dose-limiting toxic effect was myelosuppression, there were fewer dose modifications than with the four-drug regimen of Bunn et al (13). This was probably due to differences in drug dose and scheduling (18,19). Our regimen used more 5-FU and less doxorubicin, mitomycin, and semustine per 8 weeks. For cycles 1, 2, and 3 in the study of Bunn et al there were 28%, 67%, and 75% dose level modifications compared with 21%, 16%, and 20% for the FAMMe regimen.

The complete plus partial response rate for patients with adenocarcinoma of the stomach with no chemotherapy prior to this study was 39%. This is similar to the 42%–55% response rate to FAM (5-FU, doxorubicin, and mitomycin) reported by several groups (7,12,20). 5-FU, doxorubicin, and nitrosourea combinations have resulted in response rates of 52% (9). Regimens without doxorubicin for advanced gastric cancer employing 5-FU plus a nitrosourea or mitomycin produced response rates of 24%–40% (4,8).

For adenocarcinoma of the pancreas our partial response rate of 22% was disappointing. Response rates to FAM chemotherapy of 37%–40% have been reported (11,20). 5-FU, doxorubicin, and nitrosourea combinations have resulted in response rates of 26%–43% (6,10). Regimens without doxorubicin for advanced pancreatic cancer employing 5-FU plus a nitrosourea produce response rates of 12%–27% (5,21). It is unclear why we were unable to achieve a response rate similar to that from FAM chemotherapy for pancreatic cancer since none of our patients with pancreatic cancer had received prior chemotherapy, and the physical performance status and extent of disease were similar to the patients treated with FAM.

Sex, age, physical performance status, unresectable primary cancer, and sites of metastasis did not affect response rates for patients with adenocarcinoma of the stomach, gastroesophageal junction, and pancreas. This finding was somewhat unexpected since these patient characteristics often affect response to chemotherapy. They have been shown to affect response to 5-FU therapy in patients with advanced gastric cancer (4,22,23). In contrast to the single-drug studies, however, physical performance status and resectability of the primary cancer had no statistically significant effect on response and survival in patients with gastric cancer treated with FAM (7). The composition of our patient population may account for this unexpected finding. The effect of these patient characteristics on response and survival in patients treated with chemotherapy for adenocarcinoma of the pancreas is unclear because of insufficient published information.

We conclude that FAMMe chemotherapy can be administered in adequate doses without producing prohibitive myelosuppression. The starting dose was determined to be dose level C for most patients; for patients $\geq$ 70 years old or patients who had received pelvic or vertebral

radiation therapy, the starting dose was level B (table 2). FAMMe chemotherapy is effective for advanced gastric cancer. Because this was not a randomized comparative study of the relative effectiveness of FAMMe and FAM chemotherapy, no recommendation for the use of one regimen instead of the other for advanced adenocarcinoma of the stomach can be made. FAMMe chemotherapy cannot be recommended for advanced adenocarcinoma of the pancreas and gastroesophageal junction.

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Phase I–II Evaluation of a New Anthracycline Antibiotic, Aclacinomycin A, in Adults With Refractory Leukemia[1,2,3,4]

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Aclacinomycin A (ACM) is a new anthracycline antibiotic that produces substantially less cardiotoxicity in animals than does doxorubicin. To define the effective dose for the treatment of patients with leukemia, we treated 43 patients with acute nonlymphoblastic leukemia (ANLL) or acute lymphoblastic leukemia (ALL) using ACM administered at three dose levels. All patients had previously received extensive treatment with other chemotherapy; their median cumulative dose of prior anthracycline was 340 mg/m^2. An ACM dose of 100 mg/m^2/day given for 2 days (total dose, 200 mg/m^2) failed to produce significant bone marrow hypocellularity or remission in two patients. Total ACM doses of 300–360 mg/m^2 (100 or 120 mg/m^2/day x 3 days) produced marrow hypoplasia in 16 of 23 evaluable patients with ANLL. Overall, four of 32 patients with ANLL who received 300–360 mg/m^2 of ACM achieved complete remission for durations of 1, 5+, 6, and 15+ months. Two of nine patients with ALL achieved partial remission. Toxic effects of this therapy included severe leukopenia and thrombocytopenia, nausea, mucositis, and diarrhea. ECG abnormalities were noted in 43% of patients who were carefully monitored; however, only one patient developed a significant decrease in left ventricular ejection fraction as measured by radionuclide cardiography. ACM produced only minimal alopecia and did not cause tissue necrosis following inadvertent subcutaneous infiltration. We conclude that 300–360 mg/m^2 of ACM is an effective dose for the treatment of patients with ANLL and that further evaluation of this compound is indicated in patients who have received minimal prior therapy. [Cancer Treat Rep 66:1619–1623, 1982]

Anthracycline antibiotics used in combination with other agents can produce complete remission (CR) rates > 70% in previously untreated patients with acute nonlymphoblastic leukemia (ANLL) (1,2). However, the long-term administration of these compounds is limited by the development of cardiomyopathy, which is directly related to the cumulative dose (3). Since the anthracyclines have broad clinical utility, a major research effort has been directed toward the identification of active structural analogs that do not share the cardiotoxic effect.

Aclacinomycin A (ACM) is a new antibiotic initially isolated from strains of *Streptomyces galilaeus* by Oki et al (4). The chemical structures for ACM and the prototype anthracycline doxorubicin are presented in figure 1. Both compounds share similar planar anthraquinone rings but differ in that ACM contains three deoxy sugars as well as different substitutions at the 4, 10, 12, 14, and 5′ positions.

Preclinical evaluation of ACM has shown several important differences relative to doxorubicin. Cellular uptake of ACM occurs more rapidly than doxorubicin and final intracellular concentrations are higher (5). ACM is also a more potent inhibitor of RNA synthesis and is less mutagenic (6). In equal dosage, ACM is somewhat less effective against L1210 leukemia, Lewis lung carcinoma, and B16 melanoma; however, several in vivo studies have suggested that the cardiotoxic effect of ACM is as low as one tenth that of doxorubicin (7,8). Therefore, ACM might have a greater therapeutic index than doxorubicin.

Initial clinical trials of ACM in Japan revealed a pattern of toxic effects similar to that for doxorubicin; however, alopecia was minimal and congestive cardiomyopathy was

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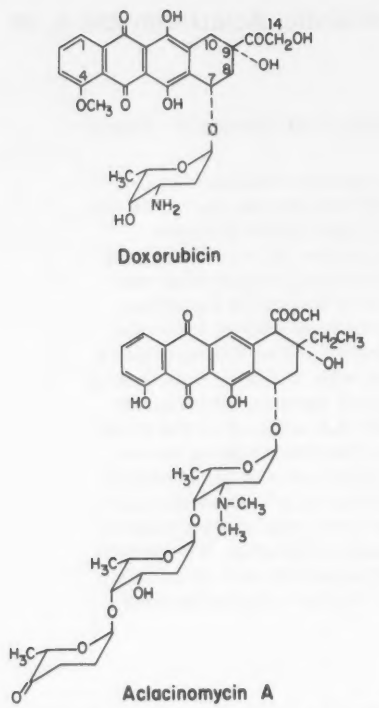

FIGURE 1.—Structural formulae of doxorubicin and aclacinomycin A.

not observed (9,10). Antitumor effects were noted in patients with malignant lymphoma and carcinomas of the breast, ovary, and bladder. Following these studies, several groups initiated clinical studies in patients with leukemia. We report here the results of a phase I–II evaluation of ACM in patients with refractory acute leukemia.

PATIENTS AND METHODS

Patients

Adult patients with acute leukemia were eligible for entry in this study after they had failed standard chemotherapy for remission induction or had relapsed from a combination chemotherapy program used for remission maintenance. All patients had adequate hepatic and renal function (serum bilirubin and creatinine $\leq$ 1.5 mg/dl). There were no restrictions on the amount of prior chemotherapy (including treatment with anthracyclines) or on initial performance status (PS). The pretreatment evaluation included a bone marrow aspirate, cbc, screening biochemical profile, ECG, and chest roentgenogram. The initial evaluation also included a gated radionuclide cardiac scan (11); however, because of these patients' low PS, it was not feasible to perform stress radionuclide angiography. Accordingly, the initial study was a resting scan which was used only to determine eligibility for protocol entry. A resting left ventricular ejection fraction (LVEF) of $\geq$ 50% was established as one of the entry criteria. Signed, informed consent was required and the study was approved in advance by the center's Clinical Investigations Committee.

Patients were monitored with the following laboratory tests: cbc and platelet count daily; serum electrolytes, BUN, and glucose every other day; and screening biochemical profile every 7 days. While in the study, most patients had daily ECGs for the first 4–5 days of treatment, and where clinically feasible, patients underwent a repeat cardiac scan following recovery of their blood cell counts. Patients achieving CR were evaluated with stress radionuclide cardiography at intervals corresponding to 300 mg/m^2 of ACM (cumulative dose).

Assessment of Response

Response to ACM was evaluated at two points during this study. First, the ability of ACM to produce bone marrow hypoplasia was evaluated by a bone marrow aspirate and/or biopsy 7–10 days after the initiation of therapy. Marrow hypoplasia was defined as hypocellularity with no evidence of leukemic blast cells. Second, patients were evaluated for their ultimate clinical response. Patients in CR were required to have a cellular bone marrow with $<$ 5% blast cells, hemoglobin $>$ 10 g/dl, peripheral wbc count $\geq$ 3500/mm^3, and platelet count $\geq$ 100,000/mm^3. A partial response was defined as $\leq$ 10% bone marrow blast cells with the same peripheral blood cell criteria.

Treatment Protocol

Patients were entered in this study at three dose levels. The initial level represented twice the dose established by Casper et al (12) in a phase I study for the treatment of patients with solid tumors. Hospitalization was required for all patients receiving the induction chemotherapy. The prescribed dose of ACM was dissolved in 50 ml of a 5% dextrose solution and was administered as an iv infusion over 30–60 minutes.

RESULTS

Thirty-four patients with ANLL and nine patients with acute lymphoblastic leukemia (ALL) were entered in this study. The characteristics of the patients with ANLL are presented in table 1. All patients had received extensive prior chemotherapy for leukemia. All but two patients had had prior exposure to other anthracycline antibiotics (principally daunorubicin); the median cumulative dose of prior anthracycline was 340 mg/m^2. Less than one half of the patients had an outpatient PS at the time of entry (ie, Karnofsky PS $\geq$ 50). Fourteen patients (41%) were

TABLE 1.—Characteristics of patients with ANLL treated with ACM

Characteristic	
Median age, yrs (range)	41 (18–75)
No. of patients with Karnofsky PS of:	
50–60	16
30–40	18
Median No. of previous induction attempts (range)	2 (1–6)
Median No. of relapses (range)*	1 (1–4)
Median cumulative dose of prior anthracycline, mg/m² (range)	340 (0–580)

*Data exclude 5 patients who had never previously achieved remission.

receiving three or more antibiotics at the time of entry and 11 (32%) had immediately failed an induction attempt with combination chemotherapy. Twenty patients (59%) were treated with ACM at their first relapse; five had never achieved remission despite at least two attempts with other intensive combination chemotherapy programs (1,13). One patient was treated after relapsing from bone marrow transplantation.

Three dose levels were examined during this study (table 2). At a dose of 100 mg/m²/day x 2 days (200 mg/m²), two patients developed marked leukopenia (ie, wbc count < 500/mm³), but neither achieved a significant degree of marrow hypocellularity or clinical remission. Sixteen patients then received 100 mg/m²/day x 3 days (300 mg/m²). At this level, ten of 15 evaluable patients achieved marrow hypoplasia and three achieved CR. In an effort to increase the percentage of patients achieving marrow hypoplasia, a final dose level of 120 mg/m²/day x 3 days was initiated. Six of eight evaluable patients at this level developed hypoplasia and one patient has had a CR.

Allowing no exclusions, four of 32 patients with ANLL who received ≥ 300 mg/m² of ACM achieved CR, for an overall CR rate of 13%. Despite the extensive prior therapy with other anthracyclines, 16 of 23 evaluable patients (70%) developed marrow hypoplasia at the two highest dose levels. Seven patients died within the first week of therapy before the marrow effects of ACM could be assessed; none of these deaths were believed to be drug-related. (Three patients died from hemorrhage, three died of sepsis, and one died from aspiration pneumonia.) Two other patients (both at the 300-mg/m² level) achieved a remission bone marrow but their platelet count failed to increase to ≥ 100,000/mm³. One of these patients died on Day 30 from an intracranial hemorrhage; the other died on Day 88 of fungal endocarditis. Neither patient had evidence of leukemia at the time of death. The median time needed to achieve marrow remission was 24 days (range, 19–30). We have only limited information regarding the activity of ACM in patients with ALL; to date, two of nine heavily pretreated patients with generally poor PS have achieved partial responses at a dose of 300 mg/m².

Patients achieving CR underwent "consolidation" therapy with ACM, receiving their induction dose again 6–8 weeks later. Patients in remission were maintained on ACM as a single agent, usually receiving 100 mg/m² every 3 weeks as outpatients. Two patients have received cumulative doses of ACM totaling 1100 and 2100 mg/m², having previously received 360 and 180 mg/m² of daunorubicin, respectively.

Toxicity

As expected, myelosuppression was severe. All patients who received ≥ 300 mg/m² (total dose) developed profound neutropenia and thrombocytopenia, and all patients required platelet transfusions and parenteral antibiotics.

Thirty-seven patients with either ANLL or ALL who received ≥ 300 mg/m² were closely monitored with daily ECGs during their first 4–5 days of treatment. As noted in table 3, 16 of those individuals (43%) developed transient ECG abnormalities consisting of T-wave inversion or ST-T segment depression. These abnormalities were not associated with symptoms and generally reversed within the first week of therapy. One 20-year-old patient developed dyspnea, interstitial pulmonary infiltrates, and fever after the third dose of ACM. These symptoms reversed following the administration of diuretics and antibiotics. Although not confirmed, it was believed that this episode was related to transient left ventricular failure induced by ACM. A followup cardiac scan was obtained on this individual but no interval decrease in his

TABLE 2.—Response of patients with ANLL to ACM

Dose level (mg/m²)	No. of patients	No. of early deaths*	No. aplastic/No. evaluable	No. of CRs	Duration of CRs (mos)
100 × 2	2	0	0/2	0	
100 × 3	16	1	10/15	3	1, 6, 15+
120 × 3	16	6	6/8	1	5+

*Occurring < 7 days from start of therapy.

TABLE 3.—Toxic effects of ACM in adults with acute leukemia

Toxic effect	No. of patients (%)
ECG abnormality (n = 37)	16 (43)
T-wave inversion	11
ST-T depression	5
Arrhythmia (n = 43)	1 (2)
Mucositis (n = 43)	23 (53)
1+	18
2+	5
Diarrhea (n = 43)	11 (26)
Median peak serum bilirubin concentration, mg/dl (range): 1.5 (0.3–9.6)	

LVEF was observed. One patient with a history of hypertension developed supraventricular tachycardia 6 days after receiving his first dose of ACM; however, the relation of this effect to drug administration is doubtful.

A total of 12 patients were re-evaluated by radionuclide cardiography following the induction attempt with ACM. One patient who received 200 mg/m^2 showed a decrease in his LVEF from 58% to 42%, which was not associated with symptoms of congestive heart failure. None of the other 11 patients (all of whom received ACM doses $\geq$ 300 mg/m^2) showed any significant decrease (ie, $\geq$ 10%) in LVEF after this therapy. Neither of the two patients receiving maintenance therapy with ACM to total cumulative doses of 1100 and 2100 mg/m^2 have shown any decrease in LVEF, despite their prior therapy with daunorubicin.

Other prominent toxic effects associated with the use of high ACM doses were mucositis and diarrhea (table 3). Nausea and/or vomiting were universal on the days of therapy, but the nausea was not considered more severe than is commonly seen with other anthracyclines. Because many patients entered this trial with hepatocellular dysfunction related to prior therapy or transfusions, hepatoxicity was somewhat difficult to assess. Fourteen patients developed reversible increases in serum bilirubin concentration to levels > 2.0 mg/dl; this increase was usually associated with mild elevations in serum alkaline phosphatase activity. Alopecia was minimal and most patients had regrowth of hair during the treatment period. There were at least two occurrences of inadvertent subcutaneous drug infiltration; however, neither patient developed skin ulceration or necrosis.

DISCUSSION

We found ACM to be an effective drug for achieving bone marrow hypoplasia and CR in patients with ANLL. The CR rate of 13% is comparable to rates achieved by other investigators using doxorubicin in heavily pretreated patients, most of whom had never received other anthracyclines (14,15). Moreover, this rate is comparable to that which we recently reported for the use of AMSA in a similar patient population (16). Only one of the 43 patients entered in this trial subsequently achieved a CR with other chemotherapy, indicating the advanced and resistant state of their disease.

From our study, it appears that cumulative ACM doses of 300–360 mg/m^2 are necessary for patients to achieve CR. This closely agrees with results found by French and Japanese investigators (17,18). Both of these studies involved lower daily doses of ACM given for more prolonged periods (ie, 10–30 mg/m^2 for 10–14 days) and have shown CR rates ranging from 17% to 23% in patients who were previously treated with other chemotherapy.

The incidence of ECG abnormalities in this study is higher than that recorded by DeJager et al (18). It is unclear whether this incidence is related to closer ECG monitoring or to the differences in dose scheduling noted above. A high incidence of ECG abnormalities was recently reported following the administration of doxorubicin to individuals who were then continuously monitored for 24 hours (19). However, there is no evidence that these changes are correlated with the subsequent development of cardiomyopathy (3).

Despite suggestions to the contrary (20), we have found no indication in this study or a related one in patients with malignant lymphoma (21) that ACM lacks cross-resistance to other anthracyclines. This finding agrees with in vitro studies (22).

ACM was brought to clinical trial with the hope that it could equal or exceed the current therapeutic results of other anthracyclines with reduced toxicity. A randomized trial comparing ACM to other anthracyclines will be required to finally decide these issues. However, results from three studies now suggest that ACM is probably as effective as other analogs in the treatment of relapsed leukemia (17,18). These studies have also shown a very low incidence of cardiotoxicity as well as a lack of alopecia and tissue necrosis after subcutaneous extravasation. Further evaluation of this agent, both alone and in combination, is clearly warranted in minimally pretreated patients with acute leukemia.

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Vomiting Induced by Cyclophosphamide and Phosphoramide Mustard in Cats[1,2,3]

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Cyclophosphamide and phosphoramide mustard produce significant vomiting. Cyclophosphamide is metabolized to phosphoramide mustard, which may ultimately contribute to vomiting after cyclophosphamide administration. The role of the chemoreceptor trigger zone (CTZ) in vomiting caused by these agents is unknown. We studied the emetic syndromes produced by iv and intracerebroventricular cyclophosphamide and phosphoramide mustard in unanesthetized normal and CTZ-ablated cats. Iv cyclophosphamide produced vomiting unpredictably, with a mean latency of 54 ± 9 mins (mean ± SE) in cats that vomited. A dose-response relationship was found for phosphoramide mustard-induced emesis. A dose of 200 mg/kg was consistently effective, with a mean latency of 127 ± 6 mins. Neither agent produced predictable emesis by the intracerebroventricular route of administration. One of four CTZ-ablated cats vomited after 300 mg/kg of cyclophosphamide. Since cyclophosphamide was an unpredictable emetic stimulus, it was not possible to further evaluate the effect of CTZ ablation on cyclophosphamide-induced vomiting. However, CTZ-ablated cats given 200 mg/kg of phosphoramide mustard vomited significantly less frequently ($P = 0.05$ by chi-square test) and with a longer latency than nonablated animals. A temporary, severe neurotoxic reaction was observed in cats receiving ≥ 300 mg/kg of cyclophosphamide, which may have had an inhibitory effect on emesis. Phosphoramide mustard was found to be a potent emetic stimulus in cats and may contribute to the emetic response following cyclophosphamide administration. Analysis of latency data suggests that in the cat other cyclophosphamide metabolites may also contribute to the emetic syndrome. [Cancer Treat Rep 66:1625–1629, 1982]

Nausea and vomiting occur very frequently after high-dose cyclophosphamide treatment (1–3). The mechanism of this emetic syndrome is unknown. A recent study of nausea and vomiting in 25 patients who received 50–75 mg/kg of cyclophosphamide by iv infusion demonstrated a 6–12-hour delay in symptom onset after drug administration (4). The prolonged vomiting latency after cyclophosphamide administration may be related to its metabolism. Cyclophosphamide itself demonstrates negligible cytotoxicity but is converted in the liver to cytotoxic metabolites (5). It has been suggested that the metabolite, phosphoramide mustard, produces emesis after cyclophosphamide treatment (5). The prolonged latency could be related to the time required for production of phosphoramide mustard, which was a potent emetic stimulus in clinical trials (6).

Vomiting resulting from a variety of drugs, including some cytotoxic agents, is mediated by the medullary chemoreceptor trigger zone (CTZ) (7,8). Vomiting may also be mediated by central and peripheral afferents to the vomiting center bypassing the CTZ (7). The role of the CTZ in vomiting caused by cyclophosphamide and phosphoramide mustard has not been established. In studies on the related compound mechlorethamine, however, Borison et al (9) were able by CTZ ablation to prevent emesis in the dog but not in the cat (9). Thoracic spinal cord transection, vagotomy, and abdominal sympathectomy were sufficient to prevent emesis in the cat.

We report here our studies on emesis after iv and intracerebroventricular (icv) administration of cyclophosphamide and phosphoramide mustard in cats. We show that phosphoramide mustard is a more potent emetic stimulus than cyclophosphamide in the cat. We suggest that vomiting caused by cyclophosphamide in the cat may not be solely related to circulating phosphoramide mustard. CTZ abla-

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tion significantly changed the course of emesis caused by phosphoramide mustard. Since cyclophosphamide was not a good emetic stimulus in the cat, we could not make a definite judgment on the role of the CTZ in emesis produced by this agent.

METHODS

Forty healthy adult cats were used for these studies. Surgical procedures were performed with sterile technique using xylazine and pentobarbital anesthesia. A combination of penicillin and streptomycin was routinely injected im postoperatively. Animals were fully recovered from surgery before use. Unless otherwise noted, animals received one drug dose and were killed at the end of the observation period.

We attempted to determine the dose-response relationship between iv cyclophosphamide and phosphoramide mustard and emesis. Initial doses were based on the reported frequency of vomiting after administration of cyclophosphamide and phosphoramide mustard in man (4,6). Depending on the vomiting response to the initial dose, drug doses were incrementally increased or decreased to determine the dose-response relationship. For iv evaluations of cyclophosphamide, a jugular venous catheter was inserted in each cat at least 48 hours prior to cyclophosphamide infusion through the indwelling catheter. Phosphoramide mustard was administered by bolus iv injection. We gave cyclophosphamide by indwelling catheter infusion because of the larger volume involved and to minimize the acute toxicity noted with more rapid administration of cyclophosphamide (*see* below).

The most predictably emetic dose of each agent was then used for tests on CTZ-ablated cats to determine the effect of this lesion on the course of emesis. CTZ ablation was performed with gentle thermal cauterization as described in a previous publication (10). Failure to vomit after 160 μg/kg of lanatoside C iv confirmed the success of CTZ ablation (11). CTZ-ablated animals were Formalin-perfused for histologic confirmation of the lesions (12).

Icv injections were made in an attempt to produce emesis predictably by another route of administration. For icv injections, cats were provided with an intracranial cannula placed stereotaxically in the right lateral ventricle (13). Vomiting induced by the injection of apomorphine (0.25 mg in 0.25 ml) served as a functional confirmation of proper cerebroventricular cannulation. Icv injections were delivered in 0.25–0.75 ml. The drug dose was incrementally elevated until overt drug effects were seen. Animals were then observed for 24 hours. Cannulae were flushed with saline at the end of the observation period. These cats fully recovered from an icv drug administration and were subsequently given higher doses.

An emetic response was scored as an all-or-none event characterized by the expulsion of gastric contents. Response latency was measured as the time between initiation of drug injection and the first emetic event. Initially, animals that received iv cyclophosphamide were observed overnight for emesis. When it became clear that late emesis did not occur if an animal had not vomited within 3 hours, a cutoff observation period of 3 hours was established. If emesis occurred within 3 hours, cats were observed for several hours thereafter to further characterize the emetic course. Cats that received iv phosphoramide mustard were observed for a minimum of 6 hours. As noted above, animals that received icv injections were observed for 24 hours.

Cyclophosphamide was contributed by Mead Johnson Incorporated and phosphoramide mustard by James C. Craddock of the National Cancer Institute. Drugs were dissolved in saline just prior to administration.

RESULTS

Iv Drug Administration

Table 1 shows the relationship between increasing doses of cyclophosphamide and phosphoramide mustard and vomiting. Cyclophosphamide failed to produce emesis reliably at any dose level but phosphoramide mustard showed a dose-response relationship.

Since cyclophosphamide did not produce consistent vomiting we have combined the entire sample of cats for further analysis of the vomiting latency. Cyclophosphamide over a dose range of 150–450 mg/kg iv produced vomiting in four of 17 cats, with a latency of 54 ± 9 mins (mean ± SE). Cats vomited one to three times over a maximal period of 4 hours from the start of the infusion. By comparison, a 200 mg/kg dose of phosphoramide mustard iv produced predictable vomiting in four of four animals, with a mean latency of 127 ± 6 mins. Cats vomited three to six times over the 6-hour observation period.

Licking movements and salivation were noted 5 mins after initiating administration of both drugs at all doses. In one animal given 750 mg/kg of cyclophosphamide and in three given 200 mg/kg of phosphoramide mustard, there was gagging and a single vomiting episode within 3–4 mins after the start of drug administration. Since repeated vomiting developed 2 hours after drug administration, we have chosen to enter the longer latency in the tables, and the prompt effects were considered to be spurious events.

Urinary frequency developed in all cats approximately 1 hour after initiation of cyclophosphamide administration. All three animals autopsied showed a severe hemorrhagic cystitis. Although urinary frequency was not noted with phosphoramide mustard, both animals autopsied after a dose of 200 mg/kg showed hemorrhagic cystitis.

An unexpected finding in all cats that received ≥ 300 mg/kg of cyclophosphamide was a profound neurotoxic effect. This was characterized by head bobbing, broad-based stance, and falling. It was first noted 10 mins after

TABLE 1.—Cyclophosphamide- and phosphoramide mustard-induced emesis in cats

Dose (mg/kg iv)	No. of cats tested	No. that vomited	Latency (mins)	Other
Cyclophosphamide				
150	4	1	45	Licking, salivation
300	6	2	54, 38	Licking, salivation, neurotoxicity
450	4	1	79	Licking, salivation, neurotoxicity
600–700	3	0	—	Licking, salivation, neurotoxicity, early emesis in 1 cat
Phosphoramide mustard				
50	2	0	—	Licking, salivation, hyperpnea
100	4	2	120, 360	Licking, salivation, hyperpnea
200	4	4	122, 126, 115, 144	Licking, salivation, early emesis in 3 cats, hyperpnea

the initiation of the infusion, increased in severity over the next 20–30 mins, and resolved over 1–2 hours. This was not seen with phosphoramide mustard but all animals did develop hyperpnea with drug administration, which resolved over 2–3 hours.

Icv Drug Administration

Neither cyclophosphamide nor phosphoramide mustard was an effective emetic stimulus by the icv route of administration but both had significant toxicity. A dose of 1.0–2.0 mg of cyclophosphamide failed to produce emesis in two cats tested. Licking and salivation were not evident. However, neurotoxic reactions characterized by nystagmus, broad-based stance, and falling was noted immediately after injection and resolved over 5–10 mins. The animals recovered fully. Phosphoramide mustard at doses of 0.025–5.0 mg produced emesis in only one of 11 trials. This was a single emetic episode after a dose of 0.75 mg. There was no vomiting at higher doses. Neurotoxic effects, licking, and salivation were produced in all cats at doses $\geq$ 0.75 mg. At doses $\geq$ 2.5 mg, cats developed anorexia, malaise, hyperpnea, extremity weakness, and spasticity. These doses were fatal in two cats at 35 hours, and animals were subsequently killed at 24 hours.

Since vomiting was not produced predictably by icv cyclophosphamide or phosphoramide mustard, CTZ-ablated animals were not tested using this route of administration.

Effect of CTZ Ablation on Vomiting

Table 2 shows the effect of CTZ ablation on emesis after administration of 300 mg/kg of cyclophosphamide or 200 mg/kg of phosphoramide mustard. One of four CTZ-ablated cats vomited after receiving cyclophosphamide, suggesting that CTZ ablation does not abolish emesis caused by this agent. However, since cyclophosphamide was a poor emetic stimulus and the number of cats that vomited was small, the effect of CTZ ablation on cyclophosphamide-induced emesis is not clear. Table 2 definitely shows that CTZ ablation did not totally prevent emesis after injection of phosphoramide mustard either. Nevertheless, the difference in the number of cats that vomited is statistically significant at the 0.05 level of probability by chi square.

The vomiting latency in the one CTZ-ablated animal that vomited in response to phosphoramide mustard was significantly longer than the emetic latency in intact animals. We observed no spurious early gagging or vomiting response to phosphoramide mustard in the CTZ-ablated animals. Two of three CTZ-ablated animals developed myoclonic jerks and dystonic posturing coincident with drug infusion. This resolved in 3 mins. One of these two animals was the only CTZ-ablated animal to vomit.

DISCUSSION

Emetic Activity

Iv cyclophosphamide produced vomiting in cats, with a mean latency of 54 $\pm$ 9 mins and a maximum duration of about 4 hours. The vomiting in man after large doses of iv cyclophosphamide has a latency of 6–12 hours and lasts 12–18 hours (4). In man the half-life of cyclophosphamide is about 7 hours (14). Although we do not know the half-life of cyclophosphamide in the cat, half-lives of 15–60 minutes have been reported for most animals examined (5). It has been proposed that the hemorrhagic cystitis seen after cyclophosphamide is caused by a metabolite (5). In the present study, the onset of cystitis symptoms about 1 hour after drug administration suggests that significant metabolism of

TABLE 2.—Effect of CTX ablation on emesis after iv cyclophosphamide and phosphoramide mustard in cats

Drug		No. of cats tested	No. that vomited	Latency (mins)
Cyclophosphamide (300 mg/kg)	Normal	6	2*	54, 38
	CTZ ablated	4	1*	119
Phosphoramide mustard (200 mg/kg)	Normal	4	4†	127 ± 6
	CTZ ablated	3	1†	181

*Not significant by chi-square test.
†$P = 0.05$ by chi-square test.

cyclophosphamide had taken place by that time. This further supports the position that metabolism of cyclophosphamide is much more rapid in the cat than in man. Such accelerated metabolism may explain both the rapid onset and short duration of emesis in the cat.

Why cyclophosphamide did not produce dose-dependent emesis in the cat is unclear. It is possible that the observed neurotoxic effect is a manifestation of a more general toxicity that also inhibits emesis. Since the neurotoxic reactions lasted only 1–2 hours, one might reasonably expect vomiting to increase as neurotoxicity resolved. This might not occur, however, if the metabolism of cyclophosphamide were significantly more rapid in the cat than in man, as was proposed above. In that case, the emetic potential of cyclophosphamide and its metabolites might never be realized in the cat, since their levels would be highest at a time when an inhibitory neurotoxicity was most evident. It is also possible that dose-dependent emesis did not develop after cyclophosphamide administration because the cat does not produce adequate concentrations of emetic metabolites.

Phosphoramide mustard is a more potent emetic stimulus in the cat than is cyclophosphamide. Although the phosphoramide mustard metabolite generated from cyclophosphamide is theoretically able to cause emesis in the cat, it is not certain that the emesis following cyclophosphamide administration is necessarily caused exclusively by the phosphoramide mustard metabolite. Indeed, the vomiting latency after cyclophosphamide was 54 ± 9 mins, whereas the latency after phosphoramide mustard at 200 mg/kg was more than twice as long, ie, 127 ± 6 mins. The longer latency of emesis following phosphoramide mustard suggests that in the cat, cyclophosphamide itself or some metabolite other than phosphoramide mustard may play a role in emesis. It has been proposed that 4OH cyclophosphamide is transported into cells, where it decomposes to phosphoramide mustard (14). Vomiting following cyclophosphamide in the cat may ultimately be caused by phosphoramide mustard, but the latency may be related to the form in which it enters cells. In man, pharmacokinetic studies have shown that after cyclophosphamide administration, maximum levels of phosphoramide mustard are achieved in 2–3 hours and the plasma level of this metabolite remains elevated over the next 4–6 hours (15). Phosphoramide mustard has been shown to be a potent emetic stimulus in the present study and in clinical trials in man (6). For the cats in the present study and for man, a 2-hour latency was noted between drug administration and vomiting (6). Thus, vomiting after cyclophosphamide, which has delayed onset and is protracted, could be understood in terms of its metabolism to phosphoramide mustard. It is uncertain if other metabolites may contribute to vomiting after cyclophosphamide administration in man.

The gagging and vomiting episodes observed in a few animals within 3–4 mins of cyclophosphamide and phosphoramide mustard administration do not seem to have a clinical counterpart. Prompt emesis was noted in toxicologic studies of mechlorethamine and may have been mediated by a cholinergic mechanism (16), which may contribute to the acute lethality in mice after cyclophosphamide (17). This very early emetic response may therefore be related to cholinergic effects of cyclophosphamide and phosphoramide mustard when given in very large doses and therefore may have no clinical counterpart.

Neurotoxicity

The head bobbing, broad-based stance, falling, and nystagmus seen after iv and icv cyclophosphamide in the cat have not been previously described. They may be caused by the parent compound since they are first noted 10 mins after the start of the infusion and after icv injection, where cyclophosphamide metabolism would be minimal. A similar syndrome has been reported following administration of mechlorethamine but the mechanism has not been elucidated (16). Alterations in the EEG have been demonstrated during infusions of very large doses of cyclophosphamide (18). Patients have reported neuropsychiatric symptoms during rapid cyclophosphamide infusions. (19). Myoclonic jerks and dystonic posturing were observed in two CTZ-ablated cats at the completion of bolus iv injections of 200 mg/kg of phosphoramide mustard. These symptoms resolved in 3 mins. Neurotoxicity was not reported with this compound in human clinical trials (6) or in toxicologic studies of mechlorethamine (16). The neurotoxicity produced by icv phosphoramide mustard was delayed in onset and was un-

remitting. A similar syndrome was observed with doxorubicin in the monkey and may have been related to a necrotizing angiopathy observed pathologically (20).

Role of the CTZ

We were unable to fully assess the role of the CTZ in vomiting after cyclophosphamide administration since we did not find a reliable emetic dose. However, since one of four CTZ-ablated animals vomited, the CTZ appears not to be essential for emesis after cyclophosphamide. Vomiting after phosphoramide mustard was less frequent and occurred with a prolonged latency after CTZ ablation. The vomiting observed may have been mediated by a non-CTZ mechanism. CTZ ablation failed to prevent emesis following mechlorethamine in the cat, although it did prolong the latency in a number of animals, thereby suggesting an ancillary role for the CTZ (9). On the other hand, mechlorethamine emesis in the cat was abolished by gut denervation and cord transection. This indicated that mechlorethamine acts peripherally and produces vomiting via visceral afferents. Vomiting following total-body irradiation is mediated by both CTZ and non-CTZ mechanisms (21,22). Phosphoramide mustard emesis also may be produced by more than one mechanism and, like mechlorethamine, be "radiomimetic." CTZ-mediated emesis produced by agents other than anticancer drugs typically have latencies < 30 mins (11,23–25). This is in contrast to the 120-min latency observed with phosphoramide mustard or 70-min latency reported with the CTZ-mediated emesis caused by cisplatin (8). It is possible that phosphoramide mustard and cisplatin have a slow cumulative action at the CTZ. Alternatively, these drugs may act elsewhere, producing an agent that then acts at the CTZ.

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Combination Chemotherapy With Cyclophosphamide and Ftorafur Against Advanced L1210 Murine Leukemia[1,2]

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The antitumor activity of cyclophosphamide (CP) in combination with ftorafur (FT) against advanced L1210 murine leukemia was investigated and compared with the activity of the combination of CP and 5-FU. CP at doses of 200–350 mg/kg was highly active, the most effective dose (% treated/control = 327) being 300 mg/kg. The activity of FT up to the LD10 dose and of 5-FU at 50 mg/kg was minimal (% treated/control ≤ 142). Coadministration of 200 mg/kg of FT with 100 mg/kg of CP resulted in an increase in activity as compared with the respective dose of CP alone as did the coadministration of 400 mg/kg of FT with 200 mg/kg of CP; the activities, however, were no better than that resulting from treatment with 300 mg/kg of CP alone. The coadministration of CP and 600 mg/kg of FT resulted in an increase in host toxic reactions and loss of antitumor activity, as did the coadministration of 400 mg/kg of FT with 300 mg/kg of CP. Treatment with FT at 400 or 600 mg/kg 24 hours before or after administration of CP at 200 or 300 mg/kg did not increase the activity over that occurring when the respective combinations of the drugs were coadministered. The activity of the combination of CP with 5-FU at doses previously reported to be synergistic was equal to that observed when mice were treated with 300 mg/kg of CP alone. These data suggest that FT increases the cytotoxicity of CP but that the combination is not synergistic. [Cancer Treat Rep 66:1631–1634, 1982]

The antitumor activities of cyclophosphamide (CP) and 5-FU have been studied in considerable detail. In numerous clinical trials these agents have been shown to be effective alone and in combination with other agents against a wide variety of human tumors (1–3). The combination of 5-FU and CP has shown favorable preclinical results against several tumor models (4–8); it has therefore been suggested that this combination is potentially synergistic. Ftorafur (FT) is a structural analog of 5-FU, its activity being similar to 5-FU but less myelosuppressive. The toxicity of FT is similar to that of a slow infusion of 5-FU (9). Recent reports suggest that the cytotoxicity of FT may involve metabolites of FT other than 5-FU (10,11). FT has recently been reported to be active against colorectal and breast tumors resistant to 5-FU (11). We have therefore studied the antitumor activity of FT in combination with CP to determine whether FT offers increased therapeutic advantage over 5-FU alone or in combination with CP.

METHODS

Male BDF_1 mice from Simonsen Laboratories, Gilroy, CA, were used. The mice were housed in plastic cages with woodchip bedding and allowed at least a 7-day acclimation period prior to use. All mice were allowed food and water ad libitum from the time of receipt to the end of the experiments. FT was obtained from the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD, and CP was obtained from Mead-Johnson and Co, Evansville, IN. Drugs were administered ip as a saline solution at 0.1 ml/10 g of body weight. Except where specified, all drugs were administered simultaneously via separate syringes.

Mice were inoculated ip with 10^6 L1210 murine leukemia cells from the laboratory stock, which was maintained by weekly transfer of 10^5 cells in DBA_2 mice. On Day 4 after tumor implantation, all mice were pooled in a common cage, weighed individually, and assigned to

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TABLE 1.—Antitumor activity of FT and CP against advanced ascites L1210 murine leukemia

Dose (mg/kg)			Survival	
FT	CP	No. of mice	Mean ± SE (days)	% T/C
200	0	7	8.9 ± 0.4*	124
400	0	7	9.6 ± 0.4*	134
600	0	6	10.0 ± 0.6*	140
0	100	7	13.7 ± 1.2*	200
0	200	6	16.8 ± 0.4*,†	236
0	300	20	22.7 ± 1.6*,†	327
0	350	7	20.0 ± 4.5*	282

*Significantly different ($P < 0.05$) from value for respective saline-treated control.
†Significantly different ($P < 0.05$) from value for next lower dose of respective drug.

groups of six to eight mice with a weight range of ≤ 3 g. Treatment was initiated on Day 4, the average weight of each group being used to determine the volume of drug solution to administer per mouse. Each separate experiment included a saline-treated control, the survival of which ranged from 6.9 ± 0.3 to 7.3 ± 0.2 days. In the final experiment, the average body weight of mice on Day 4 was used to determine the volume of drug solution to administer on Days 4 and 5. The experiments were terminated when all mice had died or at 45 days after the last treatment. The % T/C was calculated from the mean survival of drug-treated mice (T) and saline-treated mice (C) for the respective experiment. The survival times (days) of the groups were compared using the Student t test.

RESULTS

CP was very active against the advanced ascites L1210 murine leukemia, each successive increase in the dose up to 300 mg/kg resulting in a significant increase in activity (table 1). The 300-mg/kg dose of CP was therefore considered the maximum effective dose for this study. FT resulted in a significant increase in survival over the control at 200 mg/kg, but further increases up to the LD10 dose (12) resulted in only a slight increase in survival.

The effect of combinations of FT and CP is shown in table 2. Coadministration of 200 mg/kg of FT with 100 mg/kg of CP and the combination of 400 mg/kg of FT with 200 mg/kg of CP resulted in a significant increase in survival over that for mice treated with the respective doses of CP alone. Coadministration of 600 mg/kg of FT with 100, 200, and 300 mg/kg of CP resulted in a significant decrease in survival as compared to the values for the respective doses of CP alone. This also occurred when 400 mg/kg of FT was coadministered with 300 mg/kg of CP. Increasing the CP dose from 100 to 300 mg/kg in combination with 100 mg/kg of FT resulted in a consistent increase in survival compared with the value for FT alone but was not significantly greater from that obtained by treatment with 300 mg/kg of CP alone.

The activity of FT is thought to be due to the slow release of 5-FU. The activity of 5-FU and CP at doses previously reported to be synergistic is therefore re-

TABLE 2.—Antitumor activity of FT coadministered with CP against advanced ascites L1210 murine leukemia

Dose (mg/kg)			Survival	
FT	CP	No. of mice	Mean ± SE (days)	% T/C
100	100	6	8.7 ± 1.3*	126
200	100	7	19.7 ± 0.7*,†,‡	287
400	100	6	12.8 ± 2.0†,‡	187
600	100	6	9.8 ± 1.3*,†	143
100	200	6	16.5 ± 3.3†,§	241
200	200	6	19.0 ± 2.4†	277
400	200	7	19.9 ± 0.8*,†	278
600	200	7	12.0 ± 2.2*,†,‡	168
100	300	6	25.5 ± 0.8†,§	372
200	300	14	22.6 ± 1.7†	323
400	300	7	11.9 ± 1.7*,†,‡,§	166
600	300	7	8.6 ± 0.8*	120

*Significantly different ($P < 0.05$) from value for respective dose of CP alone.
†Significantly different ($P < 0.05$) from value for respective saline-treated control.
‡Significantly different ($P < 0.05$) from value for next lower dose of FT within same dose of CP.
§Significantly different ($P < 0.05$) from value for next lower dose of CP within same dose of FT.

TABLE 3.—Antitumor activity of 5-FU alone or in combination with CP against advanced L1210 murine leukemia

Dose (mg/kg)			Survival	
5-FU	CP	No. of mice	Mean ± SE (days)	% T/C
50	0	7	9.7 ± 0.2*	142
50	100	7	20.9 ± 1.6*,†	304
50	200	7	19.1 ± 2.8*,†	274
0	300	14	22.6 ± 1.6*,†	327

*Significantly different ($P < 0.05$) from value for saline-treated controls.
†Significantly different ($P < 0.05$) from value for group treated with 50 mg/kg of 5-FU alone.

ported for comparison (table 3). The activity of the combination of 5-FU and CP was greater than that for 5-FU alone but was only about equal to that of 300 mg/kg of CP.

Mulder et al (7) reported that simultaneous treatment with 100 mg/kg of 5-FU and CP was the optimal sequence of administration against advanced L1210 murine leukemia in CDF_1 mice. Since FT is thought to be a slow-release form of 5-FU, allowing a 24-hour interval between administration of FT and CP might ameliorate the host toxicity and thereby increase the therapeutic efficacy of the combination. However, no significant benefit in survival was obtained by allowing a 24-hour interval between treatment with 400 or 600 mg/kg of FT and 200 or 300 mg/kg of CP (table 4).

DISCUSSION

The activity of FT or 5-FU against advanced L1210 leukemia was minimal although survival time was significantly increased over that of the saline-treated controls. The lesser activities of CP at 350 mg/kg, the combination of 600 mg/kg of FT with all doses of CP, and the combination of 400 mg/kg of FT with 300 mg/kg of CP were due to toxic reactions, the deaths occurring in mice that were in a depleted state and showed no signs of tumor. Although two of the combinations of FT and CP resulted in significantly increased survival over that for the respective doses of CP alone, the resulting activity was no greater than that when 300 mg/kg of CP was used alone. The activity of the combination of 5-FU at 50 mg/kg and CP at 200 mg/kg was equivalent to that previously reported (6). Although the optimal dose of CP was the same as reported by Fernandes and Klubes (6), the activity of the 300-mg/kg dose against advanced L1210 murine leukemia was greater in our studies.

These results suggest, therefore, that FT increases the cytotoxicity of CP but does not increase antitumor activity against advanced L1210 murine leukemia over that expected from treatment with the optimal dose of CP alone.

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TABLE 4.—Effect of sequence of FT and CP administration on antitumor activity against advanced L1210 murine leukemia

Dose (mg/kg)			Survival	
FT	CP	Sequence of administration*	Mean ± SE (days)†	% T/C
400	200	FT + CP	24.4 ± 1.0	335
400	200	FT → CP	17.4 ± 2.6	239
400	200	CP → FT	15.0 ± 2.3	206
400	300	FT + CP	18.3 ± 3.5	251
400	300	FT → CP	18.8 ± 2.5‡	250
400	300	CP → FT	22.3 ± 1.9	305
600	300	FT + CP	10.0 ± 0.7	137
600	300	FT → CP	14.0 ± 2.6	192
600	300	CP → FT	11.3 ± 0.4	155

*FT + CP = simultaneous treatment on Day 4; FT → CP = FT on Day 4 and CP on Day 5; CP → FT = CP on Day 4 and FT on Day 5.
†Survival of saline-treated mice was 7.3 ± 0.2 days. Each group had 7 mice. Survival times of mice treated with same dose of FT and CP were statistically equal. Mice treated with 600 mg/kg of FT survived a significantly shorter time than those treated with the other dose combinations.
‡A 45-day survivor for this treatment was not included in mean.

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Ultrasonic Hyperthermia and Drugs as Therapy for Human Tumor Xenografts[1,2]

Nagabhusan Senapati,* David Houchens, Artemio Ovejera, Ralph Beard, and Ronald Nines[3]

Ultrasonic energy can generate controlled, local hyperthermia (42°C–43°C), and ultrasonic hyperthermia results in increased cytotoxicity of chemotherapeutic drugs for the treatment of cancer. Human breast (MX-1) and lung (LX-1) tumors implanted subcutaneously in athymic nude mice were treated with a single application of ultrasonic (670 kHz, peak intensity of 5 watts/cm^2) hyperthermia (43.0°C ± 0.5°C) for 30 minutes in combination with suboptimal doses of cyclophosphamide, melphalan, or procarbazine. Delays in the tumor growth rate and temporary tumor regression were observed. Comparison of the tumor growth rate with single modalities, ie, drug or hyperthermia alone, shows evidence of synergistic effects of the combination of ultrasonic hyperthermia and melphalan on MX-1 and of hyperthermia and procarbazine on LX-1 tumors. [Cancer Treat Rep 66:1635–1639, 1982]

The study of the therapeutic effects of heat on malignant rodent tumors dates back to the late 1920s (1). During the 1970s, controlled hyperthermia (42°C–44°C) was beginning to be recognized as a very promising antitumor agent (2,3). In recent years there have been many encouraging studies on the use of hyperthermia alone and as an adjuvant to chemotherapy and radiotherapy against various types of malignancies (4,5).

The athymic mouse is an excellent animal model for the study of chemotherapeutic agents on human tumor xenografts (6–9) in vivo and additionally can serve as a model for combined modality therapy (10). Giovanella et al (11) have reported the use of microwave-induced hyperthermia in the nude mouse/human tumor xenograft model.

Human breast (MX-1) and lung (LX-1) tumors implanted subcutaneously in athymic mice were treated with ultrasonic hyperthermia in combination with cyclophosphamide, melphalan, or procarbazine. The animal model, the methods of ultrasonic hyperthermia treatment, and the results of these studies are presented in this paper.

MATERIALS AND METHODS

Female nude mice (6–8 weeks of age) with a randombred National Institutes of Health Swiss background were supplied by the Animal Genetics and Production Branch, National Cancer Institute (NCI), Bethesda, MD.

The human tumors used in this study were MX-1 (a mammary duct cell carcinoma) and LX-1 (established from a small [oat] cell lung carcinoma). These tumors are established for chemotherapy protocol testing as a part of the preclinical tumor panel of the Division of Cancer Treatment of the NCI (12). Protocols for testing were those established by the NCI and briefly were as follows.

Tumor fragments (3-mm^3) were implanted subcutaneously in the right subaxillary region, and the tumor volume, in cubic millimeters, was calculated for an ellipsoid by the formula $V = (a^2 \times b)/2$, where a is the width and b is the length in millimeters. This can be considered a valid estimation of weight in milligrams, assuming unit density. The tumor sizes were standardized in the different groups by obtaining relative tumor weight (RW) calculated by the formula RW = Wi/Wo, where Wi is the mean tumor weight at any given time and Wo is the mean initial tumor weight at the start of treatment. For evaluation purposes, any treatment group with a relative tumor size < 42% of that in the untreated control group on any day was considered to be responsive to therapy (13), and a relative size < 1% indicated tumor regression.

Melphalan, cyclophosphamide, and procarbazine were supplied by the Drug Evaluation Branch of the NCI. All were dissolved in physiologic saline and administered on schedules as indicated in the results section. For all animals receiving both chemotherapy and hyperthermia treatment, the drugs were administered 1 hour prior to ultrasound treatment. Doses injected were selected on the basis of experimental data from this laboratory and from the NCI.

The tumor xenografts were treated by a weakly focused beam of ultrasound. The ultrasonic energy was partially absorbed in the tumor and the internal temperature of the tumor was controlled at 43.0°C ± 0.5°C. The ultrasonic energy was produced by a 1-inch-thick lead zirconate titanate disk transducer with fundamental thickness

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mode resonance at 670 kHz at the operating conditions. This transducer was carefully designed to deliver a maximum of 10 w of ultrasonic power without significant drifts or internal heating.

The ultrasonic output of the transducer was measured and calibrated by a radiation pressure gauge. At a total output of 5 w from the transducer, the axisymmetric intensity profile was measured at the focal plane by the transient thermocouple technique as shown in figure 1.

The schematic experimental setup for ultrasonic hyperthermia is shown in figure 2. The ultrasonic transducer was driven by a power oscillator with automatic gain control, and the transducer was coupled to the power oscillator by a transducer impedance matching network to maximize the load power factor and to improve the efficiency of the overall system. The power delivered to the transducer was continuously monitored by a radio-frequency directional power meter. The tumor temperature was continuously measured by a 30-gauge hypodermic needle type thermocouple positioned at a known location in the tumor. The core temperature of the tumor was controlled at 43.0°C ± 0.5°C by a temperature feedback circuit connected between the thermocouple implanted in the tumor and the power oscillator with automatic gain control.

The anesthetized nude mice were placed on a stainless steel platform with a 20-mm-diameter hole and an ultrasonic absorber placed beneath it. During insonation, the tumor, moistened with light mineral oil, was positioned on the top of the ultrasonic absorber. This design eliminates any possibility of undesirable standing waves of ultrasound in the tumor. Therefore, the ultrasonic dose levels could be precisely controlled and measured. During a typical experiment the tumor, rectal, and base temperatures were continuously monitored by a three-channel digital thermocouple readout device.

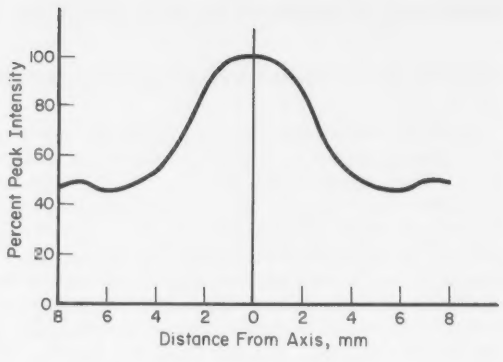

FIGURE 1.—Ultrasonic intensity distribution in water from weakly focused transducer at focal plane.

RESULTS

The measured temperature at different points inside any single tumor was observed to be within ± 0.5°C. The

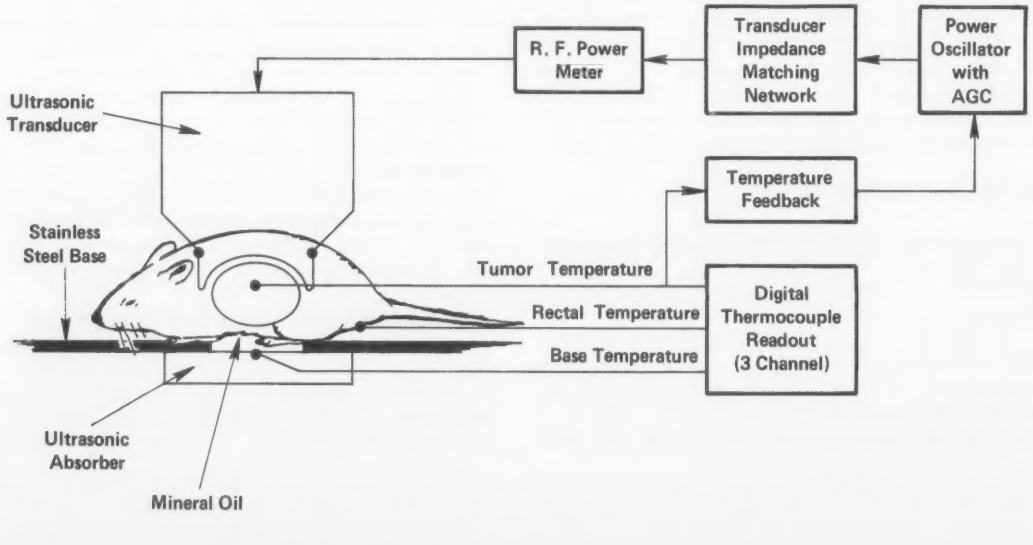

FIGURE 2.—Schematic of experimental ultrasonic hyperthermia setup.

desired temperature (43.0°C ± 0.5°C) was usually reached within 3–5 minutes from the starting time. The rectal temperature of the anesthetized mice was constant within 1°C during ultrasonic insonation (range, 25°C–27°C). This temperature is about 12°C below the normal rectal temperatures (37°C–39°C) of nude mice.

The results of the experiments are seen in table 1 and figure 3.

In experiment 1, the relative tumor size of the group that received both ultrasound and cyclophosphamide was lower on every measurement day than with either modality alone, indicating a retardation in growth, although the lowest T/C achieved was only 59%.

In experiment 2, the group receiving both melphalan and ultrasound had a marked retardation in tumor growth (T/C = 17%) for approximately 12 days, while the individual treatment modalities produced only marginal effects. The tumors in mice in the combination treatment group ultimately commenced regrowth. In an effort to establish a prolonged synergistic effect, a dose of 6 mg/kg/injection of melphalan was used in experiment 3. Marked tumor regression was effected in both the chemotherapy treatment group and the combination treatment group and no differences were seen between the two groups. To determine the effects of additional chemotherapy and hyperthermia, melphalan was given every 4 days for four injections and ultrasound was given on the days of the first and third chemotherapy treatments (experiment 4). The group receiving chemotherapy alone had a lower T/C value (28%) than the group receiving chemotherapy only in experiment 2. The group receiving two ultrasound treatments and the group receiving combination treatment had no differences in T/C values from those in experiment 2.

The LX-1 lung tumor was implanted, grown, and treated with procarbazine (experiment 5; fig 3). Procarbazine alone was not effective, while the hyperthermia treatment alone was minimally effective (T/C = 41%). The combination treatment produced marked tumor regression (relative tumor size, 0.46; T/C = 25%). The tumors in this group ultimately regrew. To determine if increased ultrasound treatment would produce more prolonged tumor regression, two treatments of ultrasound were given in experiment 6. In this experiment, the procarbazine produced some tumor retardation; the ultrasound treatment alone was effective in producing tumor retardation (T/C = 24%), while the combination treatment group had tumor regression (relative tumor size, 0.34; T/C = 9%). Ultimately, the tumors in the combination treatment group commenced regrowth at the same time as those in experiment 5.

TABLE 1.—Effects of ultrasonic insonation and/or chemotherapy on human tumor xenografts in nude mice

Experiment No.	Tumor*	Drug†	Dose (mg/kg/injection)	Drug schedule (Day)	Ultrasound schedule (Day)‡	Relative tumor size§	Optimal T/C¶ (%)
1	MX-1	Cyclophosphamide	50	20	—	3.3	85
		—	—	—	20	3.5	90
		Cyclophosphamide	50	20	20	3.3	59
2	MX-1	Melphalan	4	20,24,28	—	3.9	49
		—	—	—	20	3.6	45
		Melphalan	4	20,24,28	20	1.3	17
3	MX-1	Melphalan	6	21,25,29	—	0.32	5
		—	—	—	21	1.9	53
		Melphalan	6	21,25,29	21	0.43	6
4	MX-1	Melphalan	4	20,24,28,32	—	2.6	28
		—	—	—	20,28	1.3	58
		Melphalan	4	20,24,28,32	20,28	1.4	14
5	LX-1	Procarbazine	100	22,26,30	—	0.97	47
		—	—	—	22	0.86	41
		Procarbazine	100	22,26,30	22	0.46	25
6	LX-1	Procarbazine	100	18,22,26	—	1.20	31
		—	—	—	18,26	0.88	24
		Procarbazine	100	18,22,26	18,26	0.34	9

*3-mm^3 tumor fragments were implanted subcutaneously in right subaxillary region.

†Drugs were prepared in physiologic saline and were administered 1 hr before ultrasonic treatment except in experiment 1, in which cyclophosphamide was given 1 hr after hyperthermia.

‡An ultrasound transducer was used as described in the text to produce tumor temperatures of 43°C ± 0.5°C for 30 mins in each mouse.

§Relative tumor size = ratio of mean tumor weight of a group on evaluation day to mean tumor weight at initiation of treatment.

¶Optimal T/C (%) = lowest relative tumor size of treated group (T) as a % of relative tumor size of control group (C). T/C < 42% indicates response to therapy (13).

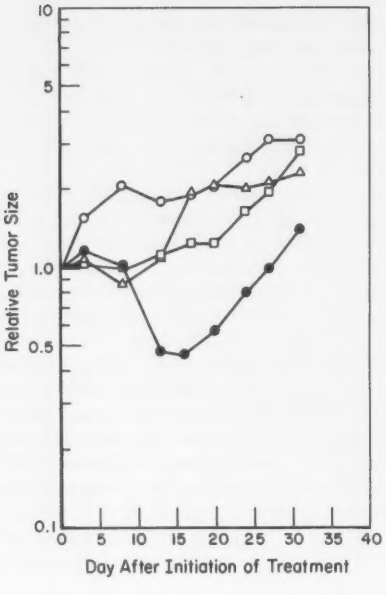

FIGURE 3.—Effect of ultrasonic hyperthermia and/or procarbazine (Pro) on LX-1 lung tumor xenografts. ○ = untreated mice (8 mice), Δ = ultrasonic insonation (5 mice, 30 mins/mouse), □ = Pro (7 mice; 100 mg/kg/; Days 22, 26, and 30 after tumor implantation), ● = ultrasonic insonation (5 mice, 30 mins/mouse) + Pro (100 mg/kg; Days 22, 26, and 30; 1st treatment 1 hr before ultrasound).

DISCUSSION

The results presented in this study demonstrated the usefulness of ultrasonic hyperthermia to treat human tumor xenografts in athymic mouse models in combination with suboptimal doses of chemotherapeutic drugs. This reduction of drug dose to achieve the same therapeutic effect is desirable. Therefore, ultrasonic hyperthermia would aid in the alleviation of undesirable toxic effects and at the same time maintain maximum efficacy.

Numerous studies to date have demonstrated significant therapeutic effects of heat in the treatment of cancer. Our research shows considerable promise for ultrasonic hyperthermia in combination with chemotherapy in the treatment of human tumors and it demonstrates the usefulness of this model for evaluation purposes. Some of the key advantages of ultrasonic hyperthermia as an adjuvant to chemotherapy are as follows:

(*a*) As shown in our results, the combination of ultrasonic hyperthermia and drug therapy has potential for synergistic effects. The mechanisms are believed to be "accelerated reaction rates" due to ultrasonic and thermal focusing of drugs.

(*b*) The heating volume and the temperature can be controlled within ± 0.5°C to conform to the shape and size of the tumor.

(*c*) During microwave and radiofrequency irradiation there is an induced artifact in the temperature-measuring process due to the interaction between the electromagnetic field and the temperature sensor. Because ultrasound is a form of acoustic energy, there is no electromagnetic artifact in the temperature measurement process.

(*d*) Ultrasound is a nonionizing radiation. To date we have found no confirmed publication in the literature on specific immunologic effects or changes in the mitotic index associated with ultrasonic exposure.

(*e*) Ultrasound is transmitted very poorly by air; hence, there is virtually no danger of exposing the operator or subject to hazardous levels of radiation. However, due to poor transmission of ultrasound in the air a coupling medium is required between the applicator and the tumor. In the present study, mineral oil has been found to be an effective medium.

The controllability, simplicity, and safety aspects of ultrasonic hyperthermia make it a promising system, and it has the advantage of treating human tumors in a proven animal model to assess the chemotherapeutic effects.

We believe this combination of ultrasonic hyperthermia and chemotherapy has the potential to achieve tumor regression at reduced dose levels and to reduce the associated side effects of the drugs in the treatment of cancer. Further development of dose, schedule, and treatment in such a model is desirable.

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Potential Cardiotoxicity With Mitoxantrone[1,2]

Frank C. Schell,* Hwee-Yong Yap, George Blumenschein, Manuel Valdivieso, and Gerald Bodey[3]

Mitoxantrone is a promising new agent developed in an attempt to find drugs with a broad spectrum of antitumor activity and devoid of cardiotoxicity. In a phase II clinical trial for refractory metastatic breast cancer, we observed congestive heart failure in four of 31 high-risk patients either during or after treatment with this drug. This report calls attention to that observation, and recommendation is made that further evaluation of this agent include careful cardiac monitoring. [Cancer Treat Rep 66:1641–1643, 1982]

Cardiotoxicity is a well-known and well-studied entity seen with several cytotoxic drugs, especially anthracyclines. It has been established that beyond certain dose levels a cardiomyopathy characterized by decreased myocardial contractility and clinical congestive heart failure will develop in a certain percent of patients treated with doxorubicin or daunorubicin (1–3).

Mitoxantrone is a new anthraquinone derivative synthesized in an attempt to develop an agent with a broad spectrum of antitumor activity and free of cardiotoxicity (4–5). Mitoxantrone showed significant activity against a number of animal tumor systems during preclinical studies (5). Available animal toxicology studies showed less cardiotoxicity than doxorubicin (6). In a recent phase II study of mitoxantrone for metastatic carcinoma of the breast refractory to conventional combination chemotherapy, we observed several patients who developed evidence of clinical congestive heart failure during or following therapy with this drug. This report calls attention to that observation and alerts the medical community to the necessity for careful and frequent cardiac evaluation in patients undergoing mitoxantrone therapy.

Thirty-one patients with refractory metastatic breast carcinoma were entered in this study. All patients had previously failed conventional combination chemotherapy, and all had previously received doxorubicin. The starting dose of mitoxantrone was 4 mg/m^2/day for 5 consecutive days, with courses repeated at 4-week intervals. During the study, four patients developed symptoms of congestive heart failure.

CASE REPORTS

Patient 1

Patient 1 was a 63-year-old white female whose breast cancer had been diagnosed 10 years previously. She had previously been treated with 5-FU, doxorubicin, cyclophosphamide, methotrexate, and tamoxifen for recurrent disease, with excellent responses. Prior doxorubicin was given to a total dose of 450 mg/m^2 and was discontinued 4 years prior to entry in the study. She was treated with mitoxantrone at a dose of 4 mg/m^2/day × 5 and achieved a complete remission after five courses. After seven courses, she developed clinical congestive heart failure with cardiomegaly, dyspnea, lower extremity edema, tachycardia, and bibasilar pulmonary rales. Chest X-ray showed evidence of congestive heart failure, ECG showed sinus tachycardia with nonspecific ST-T wave changes, and cardiac scan showed generalized hypokinesis and an ejection fraction of 0.46. She was treated with diuretics and digoxin and responded rapidly. There was no prior history of cardiovascular disease.

Patient 2

Patient 2 was a 65-year-old female who had had left mastectomy and postoperative radiation therapy 6 years previously. Prior to entry in the study, the patient was treated with 5-FU, doxorubicin, cyclophosphamide, and tamoxifen for recurrent disease, achieving a partial re-

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mission. Doxorubicin was discontinued 3 years prior to entry in the study after a total dose of 450 mg/m^2. When the patient again developed progressive disease, she was treated with mitoxantrone at a dose of 4 mg/m^2/day × 5. Due to severe myelosuppression, she required dose reduction on each of three subsequent courses. Following the fourth course of therapy she developed progressive disease and was switched to megestrol acetate. Approximately 2 months later, the patient was admitted to the hospital with acute pulmonary edema and died within 72 hours. This patient had no evidence of previous cardiovascular disease, and there were no known precipitation factors for the patient's heart failure. ECG showed marked sinus tachycardia and was otherwise unremarkable.

Patient 3

Patient 3 was a 72-year-old female who underwent mastectomy 17 years prior to entry in the study. Following 6 years of hormonal manipulations for recurrent disease, the patient began chemotherapy with 5-FU, doxorubicin, cyclophosphamide, and *Corynebacterium parvum*. Doxorubicin was discontinued 3 years prior to entry in the study after a total dose of 450 mg/m^2. Following 2 additional years of multiple chemotherapeutic agents, the patient was treated with mitoxantrone at 3.5 mg/m^2/day × 5. After four courses, she developed clinical congestive heart failure documented by physical examination and chest X-ray. ECG showed sinus tachycardia with nonspecific ST-T wave changes and cardiac scan showed generalized hypokinesis and an ejection fraction of 0.39. She responded to diuretics and digoxin. The patient's past history was significant only for mild hypertension of approximately 10 years' duration, which had been well-controlled with a low-sodium diet.

Patient 4

Patient 4 was a 31-year-old female who had had mastectomy $2^1/_2$ years previously. She had been treated with adjuvant chemotherapy including 5-FU, doxorubicin, and cyclophosphamide. Doxorubicin was discontinued after a total dose of 300 mg/m^2. One year prior to entry in the study, recurrent disease was treated with a combination of doxorubicin, mitomycin, and dibromodulcitol. After a total dose of 500 mg/m^2 of doxorubicin, she developed clinical congestive heart failure and was noted to have decreased voltage on ECG and an abnormal ejection fraction on echocardiogram. She responded well to management with digoxin and diuretics, and therapy was switched to mitoxantrone. She received 4 mg/m^2/day × 5 every 21 days for a total of nine courses, achieving a partial remission. At that time, she developed recurring symptoms of congestive heart failure documented by chest X-rays and was found to have significant hypokinesis and decreased ejection fraction documented on both serial echocardiograms and nuclear scans.

DISCUSSION

Since this study was designed to evaluate the antitumor activity of this agent and not specifically to study potential cardiotoxicity, not all patients had serial cardiac evaluation during treatment.

Nevertheless, clinical congestive heart failure was observed in four of 31 patients, which was surprising and in excess of what we would normally expect to observe in a similar population of patients in a phase II drug study. In two recent phase II studies at our institution, 77 patients taken from the same population of refractory breast cancer patients had no incidence of congestive heart failure (7,8).

Whether, in fact, congestive heart failure was directly related to the drug cannot be determined from these patients. Certainly, this population of patients carries multiple risk factors for cardiovascular decompensation, including pretreatment with doxorubicin, precordial radiation therapy, and generally poor performance status. However, that does not alter the observation that this drug is potentially cardiotoxic, whether directly or possibly synergistically with doxorubicin. Therefore, studies evaluating mitoxantrone should include careful monitoring of cardiac function to determine the incidence and severity of any possible drug-related cardiotoxicity. Although the potential for myocardial damage may exist, especially in the face of previous treatment with maximal doses of doxorubicin, mitoxantrone has shown extremely encouraging evidence of activity in early studies, and we believe that continued evaluation is certainly warranted. In 27 evaluable patients, we observed one complete and five partial remissions (9). We hope that careful study will show that even if some evidence of cardiotoxicity does exist, it will be less severe than with doxorubicin, therefore making this drug a significant addition to the cytotoxic armamentarium.

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Combination Chemotherapy With 5-FU, 1-(Aminomethyl)-3-(2-chloroethyl)-3-nitrosourea (ACNU), and Mitomycin (FUM) for Carcinoma of the Pancreas[1]

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In spite of the importance of pancreatic carcinoma, only a few chemotherapy combinations have undergone adequate trial. The combination of 5-FU, doxorubicin, and mitomycin (FAM) has been somewhat effective (1,2). Fujimoto et al (3) showed a distinct synergistic effect, "complementary inhibition" of DNA formation, between antimetabolites and 1-(aminomethyl)-3-(2-chloroethyl)-3-nitrosourea (ACNU), a newly developed water-soluble nitrosourea active against some experimental tumor systems. Based on this experiment and the enhanced therapeutic effect of a combination of mitomycin with 5-FU, we developed a combination consisting of 5-FU instead of 6-thioguanine as a purine analog, ACNU, and mitomycin (FUM), which has been evaluated in various advanced carcinomas of the gastrointestinal tract (4).

Between December 1978 and October 1981, 13 patients who had histologically documented metastatic pancreatic carcinoma with various measurable indicator lesions were treated with this protocol (table 1). An oral dose of 5-FU (200 mg) was given daily, combined with iv bolus injection of ACNU (70 mg/m^2) and mitomycin (10 mg/m^2). Chemotherapy was given until the wbc count was < 2000/mm^3 and/or the platelet count was < 75,000/mm^3, usually 14–28 days, depending on the individual bone marrow reserve. The average total dose of 5-FU was 4.2 g in each FUM course, and there was no significant difference between the dose received by responders and nonresponders. A resting period of 2–4 weeks was generally required. The whole course of chemotherapy was repeated every 6–8 weeks when the wbc count had returned to 3000/mm^3

TABLE 1.—Characteristics of 13 patients

Patient No.	Age (yrs)	Sex	Karnofsky performance status (%)	Metastatic sites	No. of courses of FUM	Response	Response duration (mos)*	Survival duration (mos)†
1	62	M	80	Liver	2	None	—	4.5
2	35	M	30	Liver	1	None	—	4
3	70	F	40	Liver, peritoneum	4	Partial‡	8§	10¶
4	61	M	100	Liver	4	Partial‡	6	8¶
5	63	F	100	Liver	4	Partial‡	8§	9¶
6	69	F	90	Liver	3	Partial‡	4.5	5
7	55	M	80	Liver	2	None	—	5
8	70	M	40	Liver	1	None	—	5
9	55	F	30	Liver, peritoneum	1	None	—	2
10	59	M	40	Liver, peritoneum	2	Partial‡	4§	6¶
11	55	M	40	Liver, peritoneum	2	None	—	3.5
12	57	F	40	Liver	2	None	—	5
13	68	M	50	Liver, lung	5	Partial‡	12§	13¶

*From the day of 50% tumor reduction until disease progression.
†From Day 1 of chemotherapy.
‡Liver metastasis responded, but patients 3, 10, and 13 had stable disease in peritoneum or lung.
§Patient still responding.
¶Patient still alive.

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and the platelet count to 100,000/mm^3. Response to chemotherapy was evaluated by previously defined criteria (2).

Six of the 13 patients (46%) responded to FUM therapy. All 13 patients had dose-limiting hematologic toxic reactions. The median lowest wbc count per course was 1200/mm^3 (range, 800–2100/mm^3) and occurred by Day 19 (range, Day 13–30), with recovery by Day 31 (range, Day 14–58). The median lowest platelet count was 41,000/mm^3 (range, 17,000–78,000/mm^3) by Day 22 (range, Day 18–29), with recovery by Day 23 (range, Day 14–35).

There has been one drug-related death due to marked leukopenia among 41 patients, including the 13 in this study, who received FUM therapy for carcinomas of the gastrointestinal tract (4). Because of this and an effectiveness equal to that of the FAM combination, we believe that FUM chemotherapy may be a promising treatment for advanced pancreatic carcinoma. A further trial in a large number of patients is warranted to determine the effectiveness of FUM therapy.

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Combination Carmustine (BCNU) and Dianhydrogalactitol in the Treatment of Primary Brain Tumors Recurring After Irradiation[1]

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The nitrosoureas have historically been the most active class of agents in the treatment of recurrent primary brain tumors (1). Of these drugs, carmustine (BCNU) appears to be the most active (2). This activity can also be demonstrated when BCNU is used with postoperative irradiation and the results are compared to those of irradiation alone (3). In a similar situation, the combination of dianhydrogalactitol (DAG) with postoperative irradiation was shown to prolong median survival as compared to that after irradiation alone (4). Combination chemotherapy containing DAG has also shown antitumor activity in recurrent brain tumors (5). The combination of BCNU and DAG has been shown to be synergistic in the Glioma 26 experimental system (6). Consequently, a phase II evaluation of the combination was conducted.

MATERIALS AND METHODS

Forty-nine patients were entered in the study, 39 of whom had histologically confirmed brain tumors. Rebiopsy was not done at recurrence, and all tumor grading was based on the original surgery. One patient was evaluable for survival only (did not return for re-evaluation after initial treatment) and five patients were ineligible (one because of prior nitrosourea therapy, two who did not have primary brain tumors, and two who had no indicator disease on computerized tomographic [CT] brain scan).

Among the 43 patients evaluable for response and survival, the median age was 48 years (range, 22–74); 27 were males and 16 were females; and 14 had an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 1, 16 had a PS of 2, and 13 had a PS of 3–4. Disease progression was evident in 27 patients in < 1 year from diagnosis and in 16 after ≥ 1 year. Median time from diagnosis to start of chemotherapy was 30.5 weeks. One patient had had prior chemotherapy (aziridinylbenzoquinone).

Tumor types and patient characteristics are shown in table 1. All patients had progressive disease (determined either neurologically and/or by CT brain scan—usually both) at entry in the study. Eligibility requirements included a wbc count $\geq 3500/mm^3$, a platelet count $\geq 100,000/mm^3$, a serum creatinine ≤ 1.5 mg/dl, a contrast-enhancing tumor mass on CT brain scan, and signed informed consent by the patient or the responsible next of kin. No patient could have received prior chemotherapy with a nitrosourea or a hexitol, primary chemotherapy with any other agent within 4 weeks, or radiation therapy within 8 weeks (unless disease progression occurred during radiation therapy—as it did in three patients).

A regression required a definite decrease in the size of the contrast-enhancing lesion on CT brain scan (not edema) coupled with neurologic improvement, provided that the latter symptoms were related to the tumor and not to surgery. Disease progression was defined as a definite increase in tumor size on CT brain scan or no change in tumor size but neurologic deterioration over two treatment cycles. Stable disease was anything else. Response determinations were made with patients receiving no corticosteroids or stable or tapering doses of corticosteroids. A neurologic examination was performed by a neurologist prior to each planned treatment. CT brain scans were done prior to the planned second treatment and then before every third subsequent treatment if regression was noted, or prior to the third planned treatment and then before every third subsequent treatment if stability was noted. Both evaluations were repeated at disease progression.

Treatment consisted of 90 mg/m^2 of BCNU given iv over 45–60 minutes plus 70 mg/m^2 of DAG given iv over 5 minutes. The first re-treatment was scheduled for 5 weeks, with subsequent re-treatments during Year 1 at 5–7-week intervals and during Year 2 at 10–12-week intervals. Treatment was discontinued at disease progression or at the end of 2 years. Drug dosages were adjusted

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TABLE 1.—Distribution of patients and regression rates for each category

Tumor types and strata	No. of patients— In study	With tumor regression
All evaluable patients	43	20 (46.5%)
Astrocytoma		
Grade 1	2	0 (0.0%)
Grade 2	13	5 (38.5%)
Grade 3	14	8 (57.1%)
Grade 4	3	1 (33.3%)
Oligodendroglioma grade 2	1	1 (100.0%)
Unbiopsied "glioma"	10	5 (50.0%)
Males	27	12 (40.9%)
Females	16	8 (50.0%)
Age		
≤ 48 yrs	22	9 (41.7%)
> 48 yrs	21	11 (52.4%)
Diagnosis to disease progression		
< 1 yr	27	13 (48.1%)
≥ 1 yr	16	7 (43.7%)
ECOG PS		
0–1	14	6 (42.8%)
2–4	29	14 (48.3%)

in an attempt to obtain wbc and platelet count nadirs < 4000 yet ≥ 2000 and < 100,000 yet ≥ 75,000, respectively. Subsequent treatment was not repeated until the wbc count had increased to ≥ 2750 and the platelet count to ≥ 95,000.

RESULTS

Tumor Response

Of the 43 evaluable patients, 20 (46.5%) had tumor regressions, 16 (37.2%) had a period of stability, and seven (16.3%) had immediate disease progression. Regression rates were not significantly different for tumor grade (1–2 vs 3–4 vs unknown), age (≤ 48 vs > 48 years), sex, time from diagnosis to disease progression (< 1 vs ≥ 1 year), or ECOG PS (0–1 vs 2–4), with $P > 0.66$ in each chi-square test of equality of proportions.

Time to Disease Progression and Survival

Overall median time to disease progression was 3.6 months. Values for median time to disease progression for patients with regression, stability, and immediate disease progression were 5.8, 2.2, and 1.1 months, respectively. Overall median survival was 7.4 months. Median survival times for patients with regression, stability, and immediate disease progression were 12.7, 5.2, and 1.9 months, respectively. None of the covariates given above for response influenced time to disease progression or survival ($P > 0.05$ in each log-rank test).

Toxicity

The median number of courses received was three (range, one to 16). Only eight patients received a total BCNU dose of > 700 mg/m^2 (range, 725–1100). These eight patients received 11.25 courses on the average (range, eight to 16).

Nausea and vomiting were mild and infrequent. No renal or pulmonary toxicity was noted. Hematologic toxicity was mild. After the first treatment, only 30% of the patients experienced leukopenia (wbc count nadir < 4000/mm^3) and only 28% had thrombocytopenia (platelet count nadir < 100,000/mm^3). Considering all courses, 54% of the patients experienced leukopenia (only 2% of the nadirs were < 2000/mm^3) and 58% had thrombocytopenia (only 10% of the nadirs were < 50,000/mm^3). Among the eight patients mentioned above, 75% had wbc counts of 2500–3500 and normal platelet counts at 6 weeks after therapy for most of the latter half of their therapy, suggesting a slowed wbc recovery. One of the eight patients had a slight rise in the SGOT (1.5 times normal), which decreased by 20% in the 2 months following completion of treatment. No treatment-related deaths were noted.

DISCUSSION

The combination of BCNU and DAG was well-tolerated by patients with primary brain tumors recurrent after

irradiation. Tumor regressions were noted in 46.5% of the patients treated. This regression rate appeared fairly constant regardless of age, sex, grade of tumor, time from initial diagnosis to disease progression, prior chemotherapy, and PS at the start of chemotherapy. When we re-evaluated the data on BCNU alone presented by Wilson et al (7), trying to include comparable tumors (ie, astrocytomas, unbiopsied "glioma," etc) and similarly stringent response criteria (ie, CT or radionuclide scan improvement plus neurologic improvement in *all* eligible patients treated), we obtained a regression rate of 21.4% (six of 28 patients). We also evaluated our nonprotocol use of BCNU in patients with similar tumors and prior chemotherapy exposure (mainly DAG), using our usual response criteria reported here. We obtained a 12.5% (three of 24 patients) regression rate. Consequently, we believe a prospectively randomized trial of BCNU plus DAG versus BCNU alone should be done and that the doses of BCNU and DAG could be safely increased to 100 and 75 mg/m^2, respectively. The response data from this study suggest that patients with recurrent "low grade" glioma and unbiopsied "glioma" could be included in such a trial if proper stratification is employed.

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Phase II Trial of *m*-AMSA in Hepatocellular Carcinoma: A Southwest Oncology Group Study[1,2]

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Twenty-three patients with hepatocellular carcinoma were treated with *m*-AMSA at a dose of 120 mg/m² iv repeated at 4-week intervals. Toxicity was primarily hematologic. Partial responses occurred in two of 14 previously treated patients and in one of nine previously untreated patients. The overall activity of *m*-AMSA in patients with hepatocellular carcinoma appears minimal. [Cancer Treat Rep 66:1651–1652, 1982]

m-AMSA is one of the large family of amino acridines synthesized by Cain and Atwell (1). The drug was selected for further study because of a broad spectrum of experimental antitumor activity in a number of murine tumors(2). Phase I clinical trials of *m*-AMSA were initiated in 1977 and several dose schedules with acceptable toxicity were identified (3,4). These studies demonstrated leukopenia to be the major dose-limiting toxic effect. In 1978, the Southwest Oncology Group initiated a phase II study of *m*-AMSA in patients with hepatocellular carcinoma. The dose schedule employed was that previously reported by Von Hoff et al (3). The purpose of the present paper is to report this experience.

MATERIALS AND METHODS

Patients with histologically confirmed hepatocellular carcinoma not amenable to surgical resection were eligible for the study. All patients had measurable disease, and prior therapy with either chemotherapy or radiation was allowable. Patients were divided into good- and poor-risk status, with the former group defined by the following criteria: age ≤ 65 years, no prior radiotherapy, normal tolerance to prior chemotherapy (if any), and bilirubin < 1.2 mg/100 ml. *m*-AMSA was given at a dose of 120 mg/m² in good-risk patients and 90 mg/m² in poor-risk patients. In patients with markedly abnormal liver function (bilirubin ≥ 3.0 mg/100 ml and/or SGOT greater than three times normal), the starting dose was 60 mg/m². *m*-AMSA was administered iv in 500 ml of dextrose in water over 1 hour. Courses were repeated at 4-week intervals, and dose adjustments for subsequent courses were based on nadir blood cell counts. Dose levels were: 40, 60, 90, 120, 140, 160, and 180 mg/m². Doses were altered as follows: if wbc count ≥ 3000/mm³ and/or platelet count ≥ 100,000/mm³, increase by one dose level; if wbc count < 2000/mm³ and/or platelet count < 75,000/mm³, decrease by two dose levels; and if intermediate nadir counts, no change. Cbc with platelet count, LDH, SGOT, alkaline phosphatase, and bilirubin were obtained before treatment, on Day 10 of each course, and before each subsequent course. Lesions were measured prior to each course, and BUN and creatinine readings were obtained prior to each treatment.

An adequate trial of therapy consisted of one course of *m*-AMSA with subsequent followup of 4 weeks. Standard Southwest Oncology Group response criteria were employed.

Twenty-five of 27 registered patients were eligible (the ineligible patients had metastatic adenocarcinoma of unknown primary and cholangiocarcinoma). Twenty-three patients were evaluable for response and toxicity, with the two inevaluable patients never receiving *m*-AMSA.

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RESULTS

Clinical and response data for the 23 evaluable patients are outlined in table 1. Most patients had received previous chemotherapy, and 20 had measurable disease in the liver. Most patients were symptomatic, with 20 of 23 having a performance status of 1 or 2. The median age of evaluable patients was 50 years (range, 15–68). Three patients responded, and all responses were partial. The median number of courses of *m*-AMSA administered was two (range, one to 16+). The responses observed were brief in two patients (1 and 2 mos) and lasted 18 months in a third patient. Two of the responders received 90 mg/m^2 of *m*-AMSA, and the third received 120 mg/m^2. Previous treatment status did not influence response, with two of 14 previously treated and one of nine previously untreated patients responding. The median survival was 22.5 weeks for previously untreated patients and 20 weeks for the previously treated group (Kaplan-Meier survival curves).

Toxicity was moderate and predominantly hematologic. Leukopenia ($\leq$ 3000 cells/mm^3) occurred in four of nine previously untreated and in nine of 14 previously treated patients. It was life-threatening (wbc count $<$ 1000/mm^3) in two patients, and in one patient a drug-related death secondary to infection was recorded. Thrombocytopenia was milder, with only five of 23 patients having nadir platelet counts $\leq$ 100,000/mm^3. The presence of severe hematologic toxicity (wbc count $<$ 2000/mm^3 or platelet count $<$ 50,000/mm^3) was noted in four patients, two of whom had elevations of bilirubin ($\geq$ 1.5 mg/100 ml) prior to therapy. Nonhematologic toxic effects included: nausea and vomiting (three of 23 patients), pain with *m*-AMSA injection (four), mucositis (two), and chemical cellulitis (one). Liver function abnormalities occurred in five patients and consisted of transient elevations of liver enzymes (SGOT, SGPT, and LDH) or bilirubin. No cardiac toxicity was identified.

TABLE 1.—Patient data

Treatment status	No. of patients
No previous therapy	9
Previous chemotherapy	14
Hepatic artery infusion*	5
Iv 5-FU and doxorubicin with or without miscellaneous agents	9
Sex	
Male	14
Female	9
Dose levels (mg/m^2)	
60	6
90	11
120	6
Site of measurable disease	
Liver	
Hepatomegaly	12
Liver/spleen scan, computerized axial tomographic scan, liver	7
Lung	3
Lymph node	1
Bilirubin levels (mg/100 ml)	
$<$ 1.0	13
1.0–1.5	5
$>$ 1.5	5
Response data	
Complete	0
Partial	3
None	20

*Multiple regimens employed (1 patient each): 5-FU, 5-FU + mitomycin, 5-FU + doxorubicin, streptozocin + mitomycin + 5-FU, FUDR + streptozocin + doxorubicin.

CONCLUSIONS

Three partial responses (13%; 95% confidence interval, 2.8%–33.6%) and moderate hematologic toxic reactions were seen in this study. Falkson et al (5) have reported a phase II study employing *m*-AMSA at a dose of 120 mg/m^2 every 3–4 weeks. Thirty-five previously untreated patients were studied, with one partial response seen and a median survival of 13 weeks in the group. Overall, 71 patients with hepatomas have reportedly received *m*-AMSA, with five of 71 (7%) demonstrating objective responses. Goldsmith et al (6) reported a partial response in a single patient. Lightdale et al (7) described 12 patients with hepatomas treated at a similar dose schedule: no response was seen, but in three patients stable disease of varying periods was reported. It appears that *m*-AMSA produces occasional tumor regression in patients with hepatomas, but overall activity appears to be minimal.

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Phase II Trial of Bisantrene for Advanced Hypernephroma[1,2]

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Bisantrene, a new guanidino-substituted anthracene derivative, has recently been brought into phase I studies, and objective tumor regression was noted in patients with hypernephroma (1–3). In addition, Von Hoff et al (4,5) demonstrated significant antitumor activity against hypernephroma in the human tumor cloning system: four of 18 patients exhibited a 70% reduction in the number of colonies and nine of 18 experienced a 50% reduction. Thus, a phase II disease-oriented trial in patients with advanced hypernephroma was undertaken at Memorial Hospital.

MATERIALS AND METHODS

Twenty-seven patients with bidimensionally measurable, pathologically confirmed hypernephroma received bisantrene. All patients had a complete medical history and physical examination, with measurement of the longest perpendicular diameters of palpable lesions by two independent investigators. Prior to each dose, a cbc, SMA-12, 5′-nucleotidase, gamma-glutamyl transpeptidase, and chest X-ray were obtained. In selected cases, liver and bone radionuclide scans and computerized transaxial tomograms (CT scans) were performed and repeated every 6 weeks. All X-rays and scans were evaluated independently (R. C. Watson). Most patients obtained a cbc 7, 10, and 14 days after each dose. Patient entry required adequate hematologic parameters (wbc count $> 4000/mm^3$; platelet count $> 150{,}000/mm^3$), Karnofsky performance status > 50%, bilirubin < 2.0 mg/100 ml, BUN < 30 mg/100 ml, creatinine < 1.5 mg/100 ml, and bidimensionally measurable lesions. Prior hormonal therapy and cytotoxic drugs were discontinued at least 3 weeks prior to the first dose of bisantrene (nitrosoureas were stopped for 6 weeks), except for methotrexate and vinblastine which were stopped at 2 weeks. An adequate trial was defined as one dose with myelosuppression and/or rapid disease progression (> 50% increase in the size of measurable lesions), or two doses with tumor progression (> 25% increase in size) and a survival of 6 weeks. Response criteria included: *partial remission (PR)*—a > 50% decrease in the summed products of the perpendicular diameters of all measurable lesions for > 1 month; *minor response*—a 25%–49% decrease in measurable lesions for > 1 month; *stable disease*—a < 25% change in tumor size for 3 months; and *disease progression*—a > 25% increase.

The drug was administered iv every 3 weeks in a slow infusion over a minimum of $1^1/_2$ hours, with monitoring of blood pressures at 10-minute intervals. In all cases, the first dose was given to patients in the supine position. Lyophilized powder was diluted to a maximal concentration of 2.0 mg/ml (range, 0.1–2.0) and infused under protection from light within 2 hours of preparation. Initially, the recommended dose was 260 mg/m², but in the absence of significant myelotoxicity, the dose was increased to 280 mg/m². One patient who had malignant hepatomegaly was started at 220 mg/m². Dose escalation by 20 mg/m² increments was permitted: of 19 patients given 260 mg/m², 14 received 280 mg/m² and five received 300 mg/m²; three of seven patients started at 280 mg/m² received 300 mg/m².

Patient Characteristics

There were 22 males and five females, with a median age of 56 years (range, 32–77) and a median performance status of 70% (range, 50%–90%). Seventeen (63%) patients had not received previous chemotherapy, while seven had received one drug and three had received more than three drugs (including anthracycline derivatives in four). Five patients had had prior irradiation, 14 had had hormonal therapy, and one had received immunotherapy. Median time from symptoms to diagnosis was 2 months (range, 0–5) and from diagnosis to protocol treatment was 8 months (range, 0–154). Primary indicator lesions were

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in the lung (16 patients); subcutaneous areas (four); abdomen, as evaluated by CT scan (five); liver (one); and lymph nodes (one). Secondary parameters included pleural-based masses (two patients), palpable abdominal masses (five), abnomal CT scans (four), a subcutaneous mass (one), malignant hepatomegaly (one), and hypercalcemia (two).

RESULTS

There were no responses (95% confidence limits, 0–12%) in 26 adequately treated patients, 16 (95% confidence limits, 0–16%) of whom had had no prior cytotoxic chemotherapy. Two patients had stable disease for 6 and 3 months, respectively. One patient who died 10 days after the first dose was considered inadequately treated.

There were 64 doses: four patients had one dose; 12, two doses; seven, three doses; two, four doses; and one, seven doses. Although five of 23 patients evaluable for acute toxic reactions experienced no side effects, nausea was observed in five (21%), vomiting in six (26%), lightheadedness in four (18%), myalgias in three (13%), fever in seven (30%), and chills in five (21%). Fever with myalgias and chills, which increased with subsequent courses, was partially blocked with diphenhydramine in three patients and completely ameliorated with corticosteroids in three. Discontinuation of corticosteroids resulted in a return of all symptoms in one patient. Four patients who were receiving concurrent corticosteroids for brain metastases or hypercalcemia experienced no side effects. One patient complained of severe shoulder pain in a contralateral arm during his third cycle which required analgesics, and another had hypotension during infusion of bisantrene which clearly was related to the rate of administration. Severe rigors and chills resulted in discontinuation of bisantrene during the third course in one patient. Local reactions including erythema and warmth at the iv site were common, and phlebitis was noted in seven patients, with significant arm swelling for 3–4 months in six. One patient given 5-FU in the same arm 2 months later had recurrence of his phlebitis. Two patients refused further therapy after developing such side effects. While no drug-related abnormalities in liver function tests were observed, one patient with extensive malignant hepatomegaly became encephalopathic 2 days after receiving bisantrene which resolved spontaneously 1 day later. There was no evidence of ECG changes or hepatic or renal dysfunction in three patients who received 1040 mg/m^2 (total, 2060 mg), 1120 mg/m^2 (2550 mg), and 1940 mg/m^2 (3608 mg), respectively.

Twenty-five patients were evaluable for hematologic toxicity. Myelosuppression was observed in 16 patients; leukopenia (< 4000 cells/mm^3) occurred in 16, and thrombocytopenia (< 150,000 cells/mm^3) occurred in four. One patient who had had no prior therapy and was given 260 mg/m^2 had dose-limiting thrombocytopenia. The wbc and platelet count nadirs were observed on Day 8, with recovery by Day 14. In 19 patients given 260 mg/m^2, nine (47%) had a wbc count < 4000/mm^3 and one (5%) had a wbc count < 2000/mm^3 (median nadir, 3400/mm^3; range, 1900–3800); two had thrombocytopenia (88,000 and 143,000 platelets/mm^3). In 19 evaluable patients given 280 mg/m^2, nine (43%) had a wbc count < 4000/mm^3 and two (17%) had a wbc count < 2000/mm^3 (median nadir, 2900/mm^3; range, 1800–3800); two had platelet counts < 150,000/mm^3. Three of five evaluable patients given 300 mg/m^2 had a wbc count < 4000/mm^3 (range, 2700–3200), but none had thrombocytopenia. No patient had significant drug-induced anemia.

DISCUSSION

Toxicity was similar to that previously reported (1–4) except that prolonged infusion of bisantrene eliminated drug-induced hypotension in all but one patient in whom blood pressure changes were clearly related to the rate of infusion. Arm swelling and chemical phlebitis were more disabling, lasting > 3 months and requiring discontinuation of the drug in two cases. Recent studies (American Cyanamid Co) have shown that crystallized bisantrene is deposited on the venous endothelium in rabbits, and both hypotension and chemical phlebitis may be ameliorated by decreasing the concentration and infusion rate of the drug. Flu-like symptoms could be prevented by a 2-day course of corticosteroids. No evidence of cardiac toxicity was noted in preclinical toxicology studies of bisantrene, and, of interest, four patients who had had prior anthracyclines and three given > 1000 mg/m^2 had no evidence of drug-induced cardiac abnormality.

In the present study, no responses occurred in 26 adequately treated patients, 16 of whom were not pretreated. In phase I trials, there was one PR for 6+ weeks among three patients given a daily dose, and one PR for 2+ months in a patient given 200 mg/m^2 (2,4). In a phase II trial with 260 mg/m^2 every 3 weeks, three of 32 patients achieved a PR.[4] Combining all results including those of the present study, only five of 62 (8%) patients achieved PR. Such poor results in vivo suggest that the in vitro human cloning assay system is, as yet, ineffective in predicting a drug's efficacy for hypernephroma. While a higher dose of bisantrene could be tried, in the dose and schedule recommended following phase I trials and used in the present study, the drug has demonstrated no efficacy against advanced hypernephroma. New drugs are still needed.

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Therapeutic Effect of Dopamine Infusion on Human Malignant Melanoma[1,2]

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Dopamine is a novel antitumor agent that has shown activity against B16 melanoma. Four patients with advanced malignant melanoma were infused with dopamine at 20 μg/kg/min for 48–120 hours. Tumor and bone marrow samples were obtained before and after treatment for comparison. Each of the patients tested showed significant reduction in the labeling index of tumor cells following treatment. These results suggest that dopamine is capable of attaining cytotoxic levels necessary to induce a biochemical inhibition of human malignant melanoma.
[Cancer Treat Rep 66:1657–1659, 1982]

Levodopa and dopamine have been shown to be effective antitumor agents in several experimental tumor systems, including melanoma (1–3). Since these agents also play a central role in melanin biosynthesis, it was anticipated that they might be effective against melanocytic tumors that contain the oxidative enzyme tyrosinase. This hypothesis was supported experimentally, since cytotoxic effects, although qualitatively similar among the various cell lines, were generally quantitatively greater in cells possessing tyrosinase.

Preclinical studies have indicated that these drugs exert a specific biochemical effect on human tumor cells as reflected in the selective inhibition of DNA synthesis. Measurements of thymidine incorporation provide a sensitive and reproducible index of the biochemical effect of these drugs that correlates with antitumor activity (4). The inhibition of thymidine incorporation has also been shown to be an indicator of response to a variety of conventional chemotherapeutic agents (5).

Since there is currently no effective therapy for the treatment of advanced malignant melanoma in man, we wished to evaluate the significance of these observations in patients with advanced disease. We sought to determine if cytotoxic levels could be achieved using dopamine and if a biochemical inhibitory effect on tumor cells in vivo as measured by thymidine incorporation could be demonstrated as a prerequisite for an antitumor response.

MATERIALS AND METHODS

Patients and Treatment Program

Four patients with histologically proven metastatic malignant melanoma for whom no other treatment was available were accepted into the study. The treatment protocol had been approved for scientific content and human protection by the appropriate institutional review boards. Patients were premedicated with propranolol, 20 mg every 4 hours, and dopamine infusions were maintained at maximally tolerable levels for 48–120 hours with constant monitoring of cardiovascular parameters. Bone marrow aspirates were taken immediately prior to and 24 hours after the initiation of therapy and processed as described below for labeling and scintillation indices. Each patient had multiple cutaneous nodules, which permitted excisional biopsy of the tumor and determination of labeling index in the biopsy specimen before and 24 hours after infusion was completed. The plasma level of dopamine was determined by high-pressure liquid chromatography.

Labeling and Scintillation Indices

The method for determination of the scintillation index in bone marrow aspirates has been described (6). Labeling and scintillation indices of the tumors were determined by a modification of the techniques reported by Murphy

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et al (5). Single cell suspensions were prepared from the tumor biopsy, and after filtration through a cotton plug, the cells were exposed to 2–10 microcuries of [^{3}H]TdR for 1 hour. An aliquot of the above suspension was cytocentrifuged and placed on microscope slides. The slides were then coated with Kodak photography emulsion NTB-2, exposed for 5 days in a dark box, and developed with G19 all-purpose fixer. Following Wright staining, the labeled cells were counted. Cells containing at least eight grains over the nucleus were counted as positive. A minimum of 1000 cells/specimen was counted and each sample was done in triplicate, with background always less than five grains per cell.

RESULTS

Toxicity

The major toxicity was related to cardiovascular effects of dopamine. All patients reported unpleasant feelings of a hyperdynamic state characterized by increased force of cardiac contractions and increased heart rate. Under no circumstances was the heart rate allowed to increase above 120 beats/minute for the duration of the infusion. Although blood pressure was kept below 150 mm systolic, it would occasionally rise above 180 mm systolic for brief periods. Patients 1 and 3 reported occipital headache during treatments. All side effects were reversible upon cessation of therapy, and each patient was discharged from the hospital 24 hours following completion of therapy. The initial plan was to re-treat patients at 1–2-week intervals; however, persistent fatigue, especially in the older patients, precluded re-treatment.

Treatment Results

Table 1 describes the results of treatment. At the maximally tolerated dose of 20 μg/kg/min, steady-state plasma concentrations between 10^{-5} M and 10^{-6} M were achieved. Comparison of the labeling index of the tumor, biopsied prior to the start of treatment and again 1 day after cessation of treatment, indicated a consistent tenfold reduction in labeling index. Bone marrow samples processed before and 24 hours after the start of infusion consistently showed a decrease in the incorporation of radioactively labeled nucleotide precursor. There was no change observed in the labeling index or in the peripheral wbc count.

DISCUSSION

Dopamine is a novel antitumor agent that has been used extensively in man for the treatment of vasomotor disorders. In the preliminary studies, the cardiovascular effects of dopamine were important in limiting the dose and potential use of dopamine as an antitumor agent. Concentrations $> 10^{-5}$ M could be achieved, which began to approximate the cytotoxic level estimated from in vitro experiments, and encouragingly, significant drops in the labeling index of tumor biopsy specimens were observed in each patient. The significance of this result is also reinforced by the simultaneous decrease in incorporation of radiolabeled nucleotide precursor into bone marrow cells. These observations are consistent with the results found in experimental leukemia models (7).

The reduction in labeling index of tumor cells, as compared to no effect upon labeling index of bone marrow cells, suggests that we might be exerting a selective biochemical inhibitory effect on tumor cells. However, the toxicity of dopamine prevented re-treatment, which might be necessary for the observation of tumor regression.

Our studies suggest that even with dopamine, one can achieve doses that approximate cytotoxic levels in humans with malignant melanoma but the dose is limited by potent vasomotor effects of the drug. With the advent of dopamine analogs, which are devoid of cardiovascular effects and can be administered at greatly increased doses, we are hopeful that this dose-limiting toxicity can be avoided. Specifically, the drug 3,4-dihydroxybenzylamine shows enhanced therapeutic activity in all experimental models, primarily through an increase in maximally tolerated dose (8).

TABLE 1.—Effect of dopamine on tumor and bone marrow in patients with malignant melanoma

Patient No.	Duration of treatment (hrs)	Plasma level (M)	Tumor (% labeling index)		Bone marrow*		
			Preinfusion	Postinfusion	TdR	CdR	UdR
1	120	4.0×10^{-5}	2.0	0.2	26	18	25
2	72	5.2×10^{-5}	3.0	0.2	25	20	25
3	48	3.5×10^{-5}	1.0	0.1	41	34	33
4	48	3.1×10^{-5}	3.0	0.2	17	25	35

*Values represent samples taken 24 hrs after infusion began and are expressed as a % of values obtained at start of infusion. Typical control values were TdR, 15,000; CdR, 800; and UdR, 1475 cpm/10^6 cells.

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Platinum Concentrations in Human Glioblastoma Multiforme Following the Use of Cisplatin[1]

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A 24-year-old female with glioblastoma multiforme was not given a nitrosourea because of interstitial lung disease. Cisplatin was administered monthly for five cycles until disease progression. A second debulking procedure was performed and tumor tissue was assayed for the presence of platinum. Levels were measurable 7 weeks after the previous course of treatment.
[Cancer Treat Rep 66:1661–1663, 1982]

The blood-brain barrier has been one of the major hindrances to the development of effective chemotherapy for malignant neoplasms of the central nervous system. Because of their high lipid solubility, the nitrosoureas have been the mainstay of treatment. Survival benefit with the use of nitrosoureas given subsequent to standard radiation therapy has been only marginal.

The recent introduction of cisplatin into clinical practice has augmented the capabilities of clinical oncologists to treat a variety of malignant tumors. Its levels are measurable in liver, lungs, kidneys, ovaries, and uterus (1–3). Distribution studies in man (4) and animals (1,2,5–8) have shown poor penetration into the central nervous system. However, studies of tumors implanted into the brains of animals have demonstrated the presence of platinum in the tumor tissue (9). Since the blood-brain barrier is violated at the time of implantation, it is difficult to extract from such studies any conclusions about platinum penetration into malignant neoplasms in man. The following is a case report of a patient with glioblastoma multiforme treated with cisplatin; concentrations of platinum were measured in the tumor 7 weeks following the last administered dose of cisplatin.

CASE REPORT

In October 1980, a grade IV glioblastoma multiforme was diagnosed in the parietotemporal area of a 24-year-old female. The patient underwent surgical debulking followed by 6000-rad irradiation. Due to a previous history of viral interstitial pneumonitis, the patient's diffusing capacity for carbon monoxide was only 39% and carmustine (BCNU) was believed to be contraindicated. The patient was therefore entered in a protocol with cisplatin at a dose of 60 mg/m^2 for 2 consecutive days every 4 weeks. She received five courses of cisplatin, with a decrease in tumor edema, decrease in midline shift, and tumor necrosis, as demonstrated by computerized tomographic scan. In view of data that suggest radiosensitization by platinum compounds (10,11), cisplatin was given on Days 1 and 28 of a 6-week course of radiation therapy.

In 5 months, the patient's tumor progressed. A second debulking procedure was performed 7 weeks subsequent to the previous dose of cisplatin. At surgery, necrotic tumor along with cystic changes were noted. Samples of both cystic fluid and tumor were removed by suction technique and assayed for platinum.

ANALYTIC METHODS

Tumor fragments were manually separated from blood and homogenized in five volumes of 0.9% NaCl. Only solid white or light pink tissue fragments were selected for homogenization. The homogenate was centrifuged at 105,000 × *g* for 60 minutes, and the supernatant (cytosol) was collected and saved. The pellet was resuspended in 0.9% NaCl and then diluted 1:1 with cold 20% trichloroacetic acid (TCA). The precipitate was sedimented by mild centrifugation. The 105,000 × *g* supernatant (cytosol) was subjected to centrifugal ultrafiltration utilizing CF-50 ultrafiltration membrane cones (Amicon Corp, Lexington, MA). The bloody matrix in which the tumor

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fragments were originally found was centrifuged for 1 minute in an Eppindorf model 5412 centrifuge to sediment any tissue fragment or cells. The clear but red supernatant was then analyzed. Cystic fluid was analyzed without further treatment. All samples (tumor fragments, cystic fluid, and blood) were analyzed for protein content by the method of Lowry et al (12) and for platinum content by atomic absorption spectrophotometry as previously described (2). The limit of detection of the analytic method for platinum is 10 ng/ml.

RESULTS

The content of platinum in various tumor fractions and in the two fluids is presented in table 1. Of importance is the low but easily detectable concentration of platinum in the tumor several weeks after the last dose of cisplatin. Also of interest is the lack of detectable platinum present in ultrafiltrates and the TCA supernatant, indicating that platinum present in the tumor and fluids is bound to high-molecular-weight molecules.

DISCUSSION

Malonato 1,2-diaminocyclohexaneplatinum-II has been the only analog of platinum detected at measurable levels in the implantable rat tumor model (9). Other analogs of platinum, including cisplatin, have been recovered in brains of experimental animals at various times after treatment (1,2,5–8). Concentrations were always low and were usually near zero by the end of the first week after treatment. Interestingly, Hoeschele and vanCamp (5) have reported an increase in brain retention of platinum in tumor-bearing relative to control animals treated with cisplatin. Lown et al (6) showed a redistribution of platinum into brains beginning 3–7 days after treatment of mice with platinum sulfate [$Pt(SO_4)_2$].

There are laboratory data to suggest that cisplatin increases radiation sensitivity (11). *cis*-Dichlorohis-(cyclopentylamine)platinum (II), an analog of cisplatin, has been proposed as a radiation sensitizer in the Chinese hamster ovary model, causing such cells to accumulate in the radiosensitive G_1 phase (13). Increasing numbers of radiosensitive G_1 cells may explain the enhanced response following cisplatin and radiation combinations (14). In addition, cisplatin given with radiation has been shown to reduce the growth rate of three solid mouse tumors when compared to radiation alone (15). It has also been demonstrated both in vitro and in vivo that therapeutic potentiation occurs if a mouse mammary carcinoma is treated with cisplatin prior to irradiation (16). Thus, because of the potential for hypoxic cell sensitization, cisplatin was given to this patient during radiation therapy.

The standard treatment of glioblastoma multiforme has been surgery followed by radiation and BCNU therapy. The present results show that when cisplatin is administered, it can cross the blood-brain barrier and enter brain tumor tissue; there, it is apparently tightly bound. Easily measurable quantities of platinum were still present in our patient 7 weeks after the last dose of cisplatin. It would appear that a malignant neoplasm of the brain is capable of violating the blood-brain barrier, allowing penetration of cisplatin into the malignant tissue.

TABLE 1.—Platinum content of tumor fractions and brain fluids

Tissue	Platinum	
	μg/g or ml	ng/mg of protein
Tumor homogenate	1.60	7.8
105,000 × *g* supernatant*	0.09	3.8
105,000 × *g* pellet†	1.54	22.9
Cystic fluid*	0.09	3.4
Blood*	0.16	—

*Ultrafiltrate had no detectable platinum.
†TCA-soluble supernatant had no detectable platinum.

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Phase II Study of DON in Patients With Previously Treated Advanced Lung Cancer[1]

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DON, an antitumor antibiotic isolated from cultures of *Streptomyces* and a structural analog of L-glutamine, functions as a glutamine antagonist (1). In an earlier phase II study of DON given daily, either orally or iv, two of nine patients with lung cancer showed apparent tumor regression (2). Because of significant mucositis and diarrhea from that schedule, DON had limited evaluation. Recently, we completed a phase I evaluation of an intermittent 3-day iv regimen (3) in which nausea and vomiting were the dose-limiting toxic effects. A dose of 160 mg/m^2 iv daily for 3 consecutive days every 3 weeks was recommended for phase II studies.

The pretreatment characteristics, drug dose and schedule of DON, survival, toxicity, and response rate are shown in table 1. Of the 21 patients with prior chemotherapy, 14 had had prior tumor regressions (eight of 15 patients with non-small cell carcinoma and six of six with small cell carcinoma). The primary lung tumor was the major indicator disease in 20 of 22 patients. Fifteen patients completed one course of treatment and were observed to have tumor progression by the first re-evaluation in 3 weeks. Three patients had less than one complete course of DON (refused further treatment because of gastrointestinal toxicity) and had no regressions. Four patients had brief periods of stability (3–12 weeks) prior to disease progression. Acute nausea, vomiting, and diarrhea were common and significant and were not well-controlled or prevented by prochlorperazine or prophylactic diphenoxylate hydrochloride with atropine sulfate. Occasional mild to moderate nausea, vomiting, diarrhea, constipation, and stomatitis were reported in the 3-week interval following DON. Interval myelosuppression was noted in 13 of the 19 evaluable patients (68%).

TABLE 1.—Characteristics, survival, toxic reactions, and response rate of patients with lung cancer treated with DON*

Characteristic	No. of patients (No. with prior chemotherapy)
Total entered	23
Total eligible and evaluable†	22 (21)
Sex	
Male	17
Female	5
Age (yrs)	
Median: 61	
Range: 46–71	
Performance status‡	
1	8
2	8
3	6
Tumor	
Adenocarcinoma	9 (9)
Squamous cell carcinoma	4 (3)
Small cell carcinoma	6 (6)
Large cell carcinoma	3 (3)
Regressions§	0
Survival (days) ¶	
Median: 107	
Range: 19–365+	
Toxic effects	
Nausea and vomiting	
Moderate: 57%	
Severe: 30%	
Diarrhea	
Mild to moderate: 30%	
Severe: 7%	
Hematologic nadirs	
Wbc count < 4000/mm^3**	9/19
Platelet count < 130,000/mm^3 ††	9/19

*160 mg/m^2 given as 10–15-min iv infusion in 50 ml of 0.9% saline, daily for 3 consecutive days every 3 weeks.

†1 patient ineligible because of gastric cancer at autopsy.

‡Eastern Cooperative Oncology Group criteria.

§Primary indications of disease: lung (20 patients), liver (1), and nodes (1).

¶Median survival in days (range) by tumor type: adenocarcinoma—71 (19–196); squamous cell carcinoma—155 (139–212+); small cell carcinoma—63 (23–115); and large cell carcinoma—121 (101–365+).

**Median wbc count nadir (range): 3000 (2100-3700); median Day (range): 12 (6–21).

††Median platelet count nadir (range): 69,000 (31,000–120,000); median Day (range): 12 (8–14).

DISCUSSION

No tumor regressions were noted among 22 patients with advanced lung cancer and one patient with advanced gastric cancer. All but one of the patients had received extensive prior chemotherapy. Two of 11 patients treated subsequent to disease progression during DON therapy had tumor regression. Nausea and vomiting were fre-

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quent and significant. Myelosuppression occurred in 68% of the evaluable courses of DON. DON, given iv on a 3-day intermittent schedule, showed significant gastrointestinal toxicity and appears to have little activity in patients with heavily pretreated lung cancers.

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Phase II Trial of Spirogermanium in Breast Adenocarcinoma: A Cancer and Leukemia Group B Study[1]

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The results of previous studies (1,2) suggest that spirogermanium, a germanium compound with cytotoxic activity, has antitumor activity in breast (1) and ovarian carcinoma (3). Phase I trials had suggested a lack of myelotoxicity (1,2,4), making this agent attractive for phase II trials.

Female patients with histologically documented breast adenocarcinoma who were not candidates for surgical resection, radiation therapy, or standard chemotherapy were eligible for the study. No patient had received more than two chemotherapeutic regimens.

Cancer and Leukemia Group B (CALGB) criteria included: (*a*) measurable disease; (*b*) ambulatory performance status (PS) ≤ 3; (*c*) total wbc count $\geq 4000/\mu l$, platelet count $\geq 100{,}000/\mu l$, serum bilirubin ≤ 1.5 mg/dl, and serum creatinine ≤ 1.5 mg/dl; (*d*) no prior therapy for 4 weeks before entry; (*e*) anticipated survival > 2 months; and (*f*) informed consent.

Patients were treated with a multidose schedule of iv infusion for 1 hour at a dose of 80 mg/m^2 (4), receiving spirogermanium on Monday, Wednesday, and Friday for 2 weeks, then twice a week, on Tuesday and Thursday, for 2 weeks. After ten treatments, patients received a single weekly infusion until disease progression occurred.

Patients were evaluated weekly for response and toxic effects, using standard criteria (5); serum electrolytes, glucose, BUN, creatinine, bilirubin, alkaline phosphatase, SGOT, and SGPT were measured every 2 weeks.

Thirty-six patients were entered in the study (table 1); four did not meet eligibility requirements and two did not receive treatment according to the specified schedule. Twenty-three patients completed a minimum of 3 weeks of therapy, with six patients receiving > 9 weeks of treatment. Death within 3 weeks of start of protocol was scored as progressive disease.

Toxic effects were noted in 50% of these patients, paralleling preclinical animal toxicology and previous phase I studies (1,2,4). Minor myelosuppression occurred in 17% of the patients (table 1). Neurologic toxicity, prominent in preclinical and phase I studies, was not dose-limiting in most patients. One patient had grand mal seizures, which may have been drug-related.

No major responses were seen among the 30 patients evaluated, indicating that spirogermanium did not have at least a 15% frequency of response at the 99% confidence level in this population.

TABLE 1.—Patient characteristics and treatment results

Characteristic	
No. of patients entered/evaluable	36/30
Age at entry (yrs)	
Mean	58.4
Range	42–78
% of patients with initial CALGB PS	
0	20
1	47
2	30
3	3
No. of dominant disease sites	
Visceral	67
Bone*	10
Soft tissue	23
% of patients with prior chemotherapy	
1 combination	45
2 combinations	55
Prior anthracycline	79
Duration of treatment (wks)	
Mean: 5	
Range: 1–9	
No. of patients with—	
CR/PR†	0
Stable disease	3
Disease progression	27
% of patients with—	
Leukopenia (≤ 3000 cells/μl)	17
Thrombocytopenia ($\leq 100{,}000$ cells/μl)	4
Congestive heart failure	4
Neurologic effects	11‡
Nausea and vomiting	17
Phlebitis	7

*Scintiscan did not show measurable disease, although it could indicate dominant disease.

†CR—complete response; PR—partial response.

‡Includes patient who had fatal grand mal seizure.

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Phase II Trial of Etoposide in the Management of Advanced or Recurrent Endometrial Carcinoma: A Gynecologic Oncology Group Study[1,2]

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Etoposide is a semisynthetic podophyllotoxin derivative. In contrast to other podophyllotoxins that are spindle poisons, etoposide appears to block entry of cells into mitosis, acting during the late S and G_2 phases of the cell cycle (1,2).

Responses have been observed in patients with lymphoma (3,4), leukemia (4,5), brain tumor (6), lung cancer (7), breast cancer (8), bladder cancer (9), etc. Toxic effects include leukopenia, thrombocytopenia, alopecia, nausea, vomiting, and diarrhea, all of which are generally reversible when therapy is discontinued. Headache, fever, and hypotension have been recorded infrequently. Recently, etoposide has been employed in combination for patients with lung cancer (10) and lymphoma (11,12).

In 1979, we reported results of phase II trials with etoposide conducted by the Gynecologic Oncology Group (GOG) in the treatment of advanced epithelial tumors of the ovary and squamous cell carcinoma of the cervix (13); two partial responses were observed in the former group (24 patients), while no responses were noted in the latter group (31 patients). A similar phase II GOG study was conducted to investigate the role of etoposide in the management of advanced or recurrent endometrial carcinoma.

Etoposide (100 mg/m^2 diluted in 150 ml of normal saline) was administered iv over a 45-minute period on Days 1, 3, and 5. The cycle was repeated every 28 days. A complete description of materials and methods is contained in an earlier paper (13).

Complete response is defined as the disappearance of all gross evidence of disease for at least 1 month. Partial response is defined as a $\geq$ 50% reduction in the product of the largest diameter and its perpendicular of each measurable lesion for a period of at least 1 month. Increasing disease is defined as a $\geq$ 50% increase in the product of the largest diameter and its perpendicular of each measurable lesion documented on two separate examinations at least 2 weeks apart or the appearance of any new lesion within 3 months of entry in the study. Stable disease is defined as a response not meeting the above criteria.

Patient characteristics, response to therapy, and adverse effects are summarized in table 1. Among 29 patients evaluated, only one partial response of 2 months' duration was noted; 13 patients had stable disease, while 15 had increasing disease. Leukopenia was the most serious adverse effect and was observed in 16 patients, with a median wbc count nadir of 2350/mm^3 (range, 250–3700). Thrombocytopenia was reported in 11 patients, with a median platelet count nadir of 94,000/mm^3 (range, 19,600–144,000).

We conclude that etoposide at the dose and schedule tested has negligible activity in patients with advanced endometrial carcinoma previously treated with combination chemotherapy.

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[2]This study was conducted by the Gynecologic Oncology Group and was supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The following institutions participated in this study: University of North Carolina School of Medicine, Chapel Hill (CA-23073); Georgetown University Hospital, Washington, DC (CA-16938); Bowman-Gray School of Medicine, Wake Forest University, Winston Salem, NC (CA-21946); Hahnemann Medical College/Jefferson Medical College, Philadelphia, PA (CA-12478); The Milton S. Hershey School of Medicine, Pennsylvania State University, Hershey (CA-16386); University of California Medical Center, Irvine (CA-23765); Indiana University Medical Center, Indianapolis (CA-21720); University of Nebraska Medical Center, Omaha (CA-23084); University of Oregon Health Sciences Center, Portland (unfunded); Duke University Medical Center, Durham, NC (CA-12534); University of Rochester Medical Center, NY (CA-12482); State University of New York, Buffalo (CA-12476); The Albany Medical College of Union University, NY (unfunded); Tufts New England Medical Center, Boston, MA (unfunded); Illinois Cancer Council, Chicago (CA-27806); University of California Medical Center at Los Angeles (CA-13630); and Albert Einstein College of Medicine, New York, NY (unfunded).
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TABLE 1. — Phase II study of etoposide in advanced endometrial carcinoma

Age (yrs)	Original stage	Previous treatment*	Mos† to etoposide	GOG performance status	Response to etoposide‡	Courses of etoposide	Toxic effects
42	IV	ADR–CTX–5-FU–Megace	16	1	ID	1	Leukopenia (2900 cells/mm^3)
44	II	RT, ADR–CTX–5-FU–Megace	22	3	SD	3	Nausea, weakness
48	IV	Provera–ADR–CTX	5	0	ID	2	—
49	IV	MELPH–5-FU–Megace	3	2	ID	1	—
53	I	RT, MELPH–5-FU–Megace, CIS	60	1	SD	12	Minimal hair loss, fatigue
54	II	RT, MELPH–5-FU–Megace, CIS	66	0	SD	7	Leukopenia (3700 cells/mm^3), nausea
54	II	RT, MELPH–5-FU–Megace	15	2	SD	2	Leukopenia (250 cells/mm^3), thrombocytopenia (19,600 cells/mm^3)
56	I	RT, ADR–CTX–5-FU–Megace	17	2	ID	1	—
57	II	RT, ADR–CTX–Provera	6	2	ID	1	—
61	I	RT, ADR, PIP	45	2	SD	2	Leukopenia (1150 cells/mm^3), thrombocytopenia (88,000 cells/mm^3), weakness, fever
62	III	ADR–CTX–5-FU–Megace	15	2	SD	4	Leukopenia (3500 cells/mm^3), thrombocytopenia (110,000 cells/mm^3), nausea, vomiting
63	IV	ADR–CTX–5-FU–Megace, CIS	11	1	ID	2	Leukopenia (2400 cells/mm^3), thrombocytopenia (107,000 cells/mm^3), alopecia
63	—	RT, Provera–Megace, ADR–CTX, CTX–Megace	124	1	SD	10	Leukopenia (2300 cells/mm^3), alopecia
63	—	RT, ADR–CTX–5-FU–Megace, PIP	51	2	ID	1	Thrombocytopenia (67,000 cells/mm^3)
64	III	RT, ADR–Megace	37	1	ID	2	—
64	IV	MELPH–5-FU–Megace	6	1	ID	1	Nausea
64	III	RT, ADR–CTX–5-FU–Megace	10	2	SD	3	Leukopenia (3200 cells/mm^3)
65	III	RT, Megace, ADR–CTX	10	1	ID	1	—
66	I	RT, MELPH–5-FU–Megace	22	2	SD	10	Fatigue, alopecia
67	I	RT, ADR–CTX–5-FU–Megace	28	1	SD	2	Leukopenia (1800 cells/mm^3), thrombocytopenia (144,000 cells/mm^3)
68	III	ADR–CTX–5-FU–Megace	11	2	PR	13	—
69	III	RT, Megace, ADR	11	2	ID	2	Leukopenia (800 cells/mm^3), thrombocytopenia (55,000 cells/mm^3), skin breakdown
69	III	Megace, Provera, ADR–CTX–5-FU–Delalutin, RT	25	2	ID	1	Leukopenia (1100 cells/mm^3)
70	I	MELPH–5-FU–Megace, RT	8	3	ID	2	Leukopenia (2500 cells/mm^3), thrombocytopenia (25,000 cells/mm^3)
73	I	RT, MELPH–5-FU–Megace	56	2	SD	8	Leukopenia (900 cells/mm^3), thrombocytopenia (104,000 cells/mm^3), anemia
74	I	RT, Provera	43	1	SD	5	Leukopenia (3168 cells/mm^3)
77	IV	MELPH–5-FU–Megace, ADR	12	0	ID	3	Thrombocytopenia (144,000 cells/mm^3), nausea

77	—	RT, MELPH–5-FU–Megace	55	3	1D	2	Leukopenia (1700 cells/mm^3), nausea, vomiting
78	III	RT, MELPH–5-FU–Megace	10	1	SD	3	Leukopenia (3500 cells/mm^3), thrombocytopenia (94,000 cells/mm^3), nausea, vomiting

*ADR = doxorubicin; CTX = cyclophosphamide; RT = radiation therapy; MELPH = melphalan; CIS = cisplatin; PIP = piperazinedione.
†From diagnosis.
‡1D = increasing disease; SD = stable disease; PR = partial response.

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Gallium Nitrate in Advanced Soft Tissue and Bone Sarcomas: A Southwest Oncology Group Study[1,2]

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Gallium nitrate, an anhydrous salt of gallium (a naturally occurring heavy metal), was reported in 1975 to have significant antitumor activity in animal systems (1). Two clinical phase I trials reporting activity in bone and soft tissue sarcomas led to the study of gallium nitrate in advanced soft tissue and bone sarcomas by the Southwest Oncology Group (2,3).

PATIENTS AND METHODS

Thirty-two patients with advanced, histologically confirmed soft tissue and bone sarcomas were entered in the study (table 1). Entrance requirements included written informed consent in accordance with institutional and FDA guidelines, life expectancy of at least 6 weeks, and normal hematopoietic, hepatic, and renal functions.

All patients were hydrated with iv fluids followed by the administration of gallium nitrate at a dose of 700 mg/m^2 as a 30-minute iv infusion. Treatments were administered at 2-week intervals. An adequate trial was defined as two courses of therapy (4 weeks).

RESULTS

Response

No complete or partial responses were observed. Gallium scans were performed in seven patients. In all seven patients, activity was noted in regions of the primary and/or metastatic site.

Toxicity

Leukopenia was mild (3–3.9 × 10^3 cells/mm^3) to moderate (2–2.9 × 10^3 cells/mm^3) in 30% of the evaluable patients. Mild nephrotoxicity (BUN 20–40 mg/100 ml; creatinine 1.2–2 mg/100 ml) occurred in 30% of the patients but was severe (BUN > 100 mg/100 ml; creatinine > 4 mg/100 ml) in only one. Nauseas and vomiting were mild to moderate in slightly more than one half of evaluable patients. Mild hearing impairment developed in one patient. Neuropathy was not observed.

TABLE 1.—Patient characteristics, histologic subgroup, and response

Characteristic	No. of patients
Total evaluable	31
Sex	
Female	12
Male	19
Age in yrs	
Median: 52	
Range: 15–78	
Histologic subgroup	
Soft tissue sarcoma	24
Bone sarcoma	7
Prior therapy	
Doxorubicin combinations	26
Other combinations	3
None	2
Radiotherapy	18
Response to gallium nitrate (700 mg/m^2)	0
Toxic effects	
Leukopenia*	10
Nephrotoxicity	
Mild†	7
Severe‡	1
Nausea and vomiting (mild to moderate)	16
Hearing impairment (mild)	1

*2–3.9 × 10^3 cells/mm^3.
†BUN 20–40 mg/100 ml; creatinine 1.2–2 mg/100 ml.
‡BUN > 100 mg/100 ml; creatinine > 4 mg/100 ml.

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DISCUSSION

This phase II study of gallium nitrate failed to demonstrate activity in patients with soft tissue and bone sarcomas. In prior clinical phase I trials (2–4), one of three patients with osteogenic sarcoma (2) and one of 17 with soft tissue sarcoma (3) showed a partial response. We conclude that, at the dose and schedule used in this study, gallium nitrate does not appear to have activity in previously treated patients with advanced soft tissue or bone sarcomas.

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Phase II Trial of Spirogermanium in Advanced Epithelial Carcinoma of the Ovary[1]

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Spirogermanium is an azaspiran-germanium compound that has had no hematologic, hepatic, or renal toxicity in phase I studies (1). Initial studies suggested antitumor activity in pretreated patients with ovarian carcinoma (2), thus prompting a phase II trial in patients with recurrent ovarian carcinoma.

In addition to giving informed consent, patients eligible for the study had to have (*a*) histologically documented inoperable or recurrent epithelial carcinoma of the ovary, (*b*) failure of a trial of standard therapy defined as an alkylating agent plus cisplatin in patients with a creatinine clearance > 60 ml/min, (*c*) Cancer and Acute Leu-

TABLE 1.—Patient characteristics and treatment results

Age (yrs)	CALGB PS	Prior treatments*	Response to spirogermanium	No. of doses of spirogermanium	Toxic effects
42	2	ALK, CTX, HMM, MTX, 5-FU, CDDP, AMSA	Disease progression	11	None
46	2	CTX, MTX, 5-FU, ADR, CDDP, HMM	Disease progression	14	None
53	2	CTX, MTX, ADR, 5-FU, HMM, CDDP	Disease progression	11	None
56	2	CTX, MTX, ADR, HMM, CDDP, 5-FU, AMSA, VINCR, BLEO	Inevaluable	3	Blurred vision
49	3	CTX, ADR, CDDP, HMM	Disease progression	11	None
49	2	CTX, ADR, CDDP, HMM	Disease progression	12	Light-headedness
49	0	CTX, CDDP, HMM	Disease progression	16	Light-headedness
44	3	CTX, ADR, CDDP, HMM, VLB	Disease progression	10	Psychosis
67	2	CTX, ADR, CDDP, HMM, MMC, MTX	Disease progression	10	None
65	2	CTX, ADR, CDDP, HMM, TAMOX, VLB	Disease progression	18	Confusion, light-headedness, agitation
72	2	CTX, ADR	Stabilization	12	Leukopenia
57	2	CTX, ADR, CDDP, HMM, 5-FU, LEUK	Disease progression	11	Light-headedness
60	1	CTX, ADR, CDDP, HMM, VLB	Disease progression	15	None
62	1	LEUK, CTX, ADR, CDDP, HMM	Disease progression	10	Light-headedness

*ALK = melphalan, CTX = cyclophosphamide, HMM = hexamethylmelamine, MTX = methotrexate, CDDP = cisplatin, VINCR = vincristine, BLEO = bleomycin, VLB = vinblastine, LEUK = chlorambucil, TAMOX = tamoxifen, MMC = mitomycin, ADR = doxorubicin.

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kemia Group B (CALGB) performance status (PS) ≤ 3 (ambulatory), (*d*) measurable disease, (*e*) expected survival > 2 months, and (*f*) total bilirubin < 1.5 mg/dl and creatinine clearance > 30 ml/min.

All patients were treated by 60-minute infusion of spirogermanium on the following schedule: three times weekly during Weeks 1 and 2, twice weekly during Weeks 3 and 4, and once weekly at Week 5 and thereafter. The initial dose level was 60 mg/m^2; in the absence of toxic effects this was escalated to 80 mg/m^2 at Week 2 (3). All patients were evaluated for toxic reactions and response on a biweekly basis. Responses were evaluated according to previously defined criteria (2).

Of the 14 patients entered in the study, all were evaluable for toxic reactions and 13 were evaluable for response.

Significant neurotoxic reactions were observed in one half of the patients treated in this group (table 1), despite administration of spirogermanium by slow iv infusion and gradual dose escalation. A previous phase I trial (3) also demonstrated lower tolerance to spirogermanium in patients with a poor PS. One patient exhibited a mild leukopenia of 3500 cells/mm^3 at Day 8, which rose to 4600 cells/mm^3 on Day 17 despite continuation of spirogermanium at full dose.

No major responses were seen in 13 consecutive evaluable patients, indicating that the therapeutic antitumor effect in previously treated patients with ovarian carcinoma is < 20%, within 90% confidence limits. This study could not confirm activity of spirogermanium in previously treated patients with ovarian carcinoma.

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Lack of Correlation Between Effects of Anthracyclines on In Vitro Cardiac Guanyl Cyclase and In Vivo Cardiotoxicity[1]

Lehotay et al (1) recently reported that anthracyclines and anthracenediones inhibited, and occasionally stimulated, rat heart guanylate cyclase in vitro. Based on the observation that daunorubicin and doxorubicin were more potent inhibitors than the less cardiotoxic compounds aclacinomycin A and 7-OMEN, the authors speculated that a quantitative or causal relationship may exist between cardiotoxicity and inhibitory activity of cardiac guanylate cyclase. Since we have tested most of the compounds in a rat cardiotoxicity model, it was of interest to determine whether or not the in vivo data fit this hypothesis.

The effects of 26 derivatives on cardiac guanylate cyclase activity are presented in table 1 together with the minimal cumulative cardiotoxic dose (MCCD) as determined in the rat model. In this experiment drugs were injected ip five times per week at two or more doses. ECGs were recorded, and the total dose causing a significant prolongation of the QRS interval was determined (2).

There was no significant correlation between in vitro enzyme inhibition and ECG effects in vivo. This is not surprising, since the pharmacokinetic complexities are not considered in the in vitro system. A case in point is the *N,N*-dimethyl analog of doxorubicin, which is a weak inhibitor of guanylate cyclase. In the intact rat it caused greater ECG changes and more serious structural damage of the heart muscle than doxorubicin. The explanation was an eightfold higher accumulation of the *N,N*-dimethyl analog in the rat hearts after 1 week of treatment (3).

The ECG changes induced in rats by doxorubicin and most of its derivatives develop gradually and, if the dose is properly adjusted, in the absence of serious general toxic effects. But with each new injection the QRS interval becomes longer. However, some compounds elicit a different response. For example, carubicin did not induce ECG changes until the rats began to die. The electron microscopic evaluation of the heart muscle also disclosed qualitative differences: instead of prominent dilatation of the sarcoplasmic reticulum, which is typical for anthracyclines, carubicin caused mainly atrophy of the myofibrils (4). Another type of response was observed with AD-32: ECG changes of the same type as seen with doxorubicin developed promptly (MCCD, 48 mg/kg), but with continued treatment almost no further deterioration of the ECG occurred. From this discussion it is evident that biologically relevant differences exist between closely related anthracyclines. These are, of course, not recognized if only one biologic quality is measured.

The hydrazone derivatives tested by Lehotay et al (1) did not inhibit, but stimulated, guanylate cyclase activity. In the rat in vivo cardiotoxicity model, these compounds had relatively weak cardiotoxic properties. Moreover, zorubicin, the most widely studied hydrazone derivative, differed from doxorubicin also with regard to its effect on heart mitochondrial function (5).

It is encouraging to note that it is now possible to measure a variety of biologic effects of anthracycline antibiotics on the heart. Although the relevance of these effects for the development of cardiomyopathy is not well-understood, it is hoped that the better ability to characterize the biologic spectrum of new anthracyclines will help in the discovery of new derivatives with more favorable margins of safety.

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TABLE 1.—Effects of test compounds on cardiac guanylate cyclase and on rat ECGs in vivo

NSC No.	Name	% change in guanylate cyclase from control*	MCCD (mg/ kg)
	Parent compounds and short-chain derivatives		
256942	4-Epi-doxorubicin	–56	16
123127	Doxorubicin	–44	11
143491	Doxorubicin 3-oxime	–24	48
263673	Daunorubicin	–23	12
180024	Carubicin	–22	*See* text
256439	Demethoxydaunorubicin	–22	3.5
149584	Doxorubicin-14-nicotinate	–21	20
268708	Daunorubicin-9-desacetyl	–13	33
	Anthracenedione derivatives		
279836	Dihydroxyanthracenedione	–24	8
196473	9, 10-Anthracenedione	–20	128
	Sugar or long-chain hydrocarbon derivatives		
246071	Doxorubicin, *N*-dodecanoyl	–8	72
261057	Doxorubicin, 14-stearoyl glycolate	–4	40
261045	Doxorubicin, *N*,*N*-dimethyl	–2	6 *(see* text)
269148	7-OMEN	+2	45
246131	AD-32	+3	48 *(see* text)
258812	Daunorubicin, *N*,*N*-dimethyl	+5	11
267703	Quelamycin	+6	11.5†
268242	Daunorubicin, *N*,*N*-dibenzoyl	+14	125
208734	Aclacinomycin A	+19	28
	Hydrazone derivatives		
146496	Daunorubicin gycoloylhydrazone HCl	+2	40
221265	Daunorubicin, *m*-nitrobenzoylhydrazone	+9	32
237672	Daunorubicin, 3,4-dichlorobenzoylhydrazone	+19	20
164011	Zorubicin	+25	24
219977	Daunorubicin, *p*-chlorobenzoylhydrazone	+26	48
233853	Doxorubicin, octanoylhydrazone	+26	40
266210	Daunorubicin, bis-succinoylhydrazone	+36	60

*Data from ref 1.

†Calculated as doxorubicin equivalents. Spearman rank correlation coefficent = 0.32 ($P > 0.1$).

Acute ECG Changes Associated With AMSA Treatment

AMSA is a relatively new acridine derivative with antitumor activity. Previous phase I and II clinical trials using this agent have revealed that myelosuppression is the major toxic side effect (1). Other side effects include nausea and vomiting, stomatitis, alopecia, local phlebitis, allergic dermatitis, hepatotoxicity, and fatigue (2–4). Acute cardiac toxicity has been reported to occur during or shortly after the administration of the drug. This toxic effect may be related to concomitant hypokalemia (5).

In two patients who were being treated with AMSA, we observed acute ECG changes that appeared to be transient and not related to electrolyte abnormalities. More importantly, these laboratory findings were not related to any clinical signs or symptoms of cardiac toxicity.

CASE REPORTS

Patient 1

A 63-year-old white male with bladder cancer metastatic to the lungs had had disease progression during prior therapy including a combination of cyclophosphamide, doxorubicin, and cisplatin. He began AMSA therapy according to a Southwest Oncology Group protocol at a dose of 90 mg/m^2 by iv infusion. No abnormalities were noted in the ECG after the first dose of 170 mg. Following the second dose, the ECGs showed a significant change. While the pretreatment study (fig 1A) was essentially normal, an ECG taken 1 hour after AMSA infusion (fig 1B) revealed ST-segment alterations and T-wave inversion consistent with anterolateral ischemia. A study 24 hours later (fig 1C) showed that the ECG had

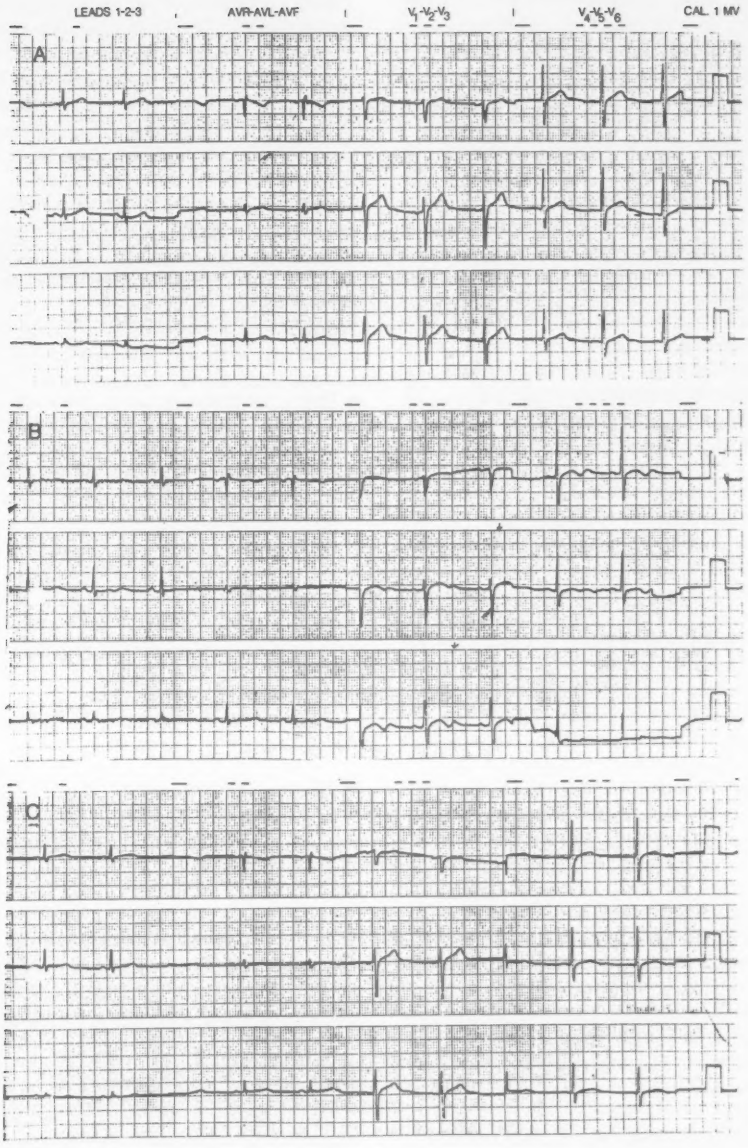

FIGURE 1.—ECGs for patient 1: prior to AMSA infusion (A), 1 hr after AMSA infusion (B), and 24 hrs after AMSA infusion (C).

reverted once again to the normal pretreatment pattern. The patient was totally asymptomatic during the drug infusion and remained so during the entire treatment period; pretreatment serum potassium was 3.6 mEq/liter.

Prior to his next dose of AMSA, the patient was admitted to the hospital and underwent extensive cardiac evaluation. His pretreatment and posttreatment ejection fractions, cardiac enzymes, electrolytes, and pyrophosphate scans were all within normal limits. Pretreatment thallium scan was abnormal but showed no change following therapy. ECGs once again showed changes consistent with anterolateral ischemia 1 hour after the patient received AMSA. The ECG again returned to normal 12–24 hours after the infusion. Cardiac monitoring was performed for 24 hours and no arrhythmias were observed. The patient remained asymptomatic during and after the treatment. He received a fourth course of AMSA; ECG showed transient ischemic changes, but there were no clinical symptoms. The total AMSA dose was 680 mg. The patient did have the expected myelosuppression following each course but had only minimal nausea. No other toxic effect was noted.

Patient 2

A patient with metastatic prostate cancer treated with AMSA in a Southwest Oncology Group protocol had similar transient ECG changes following his second course of the drug. Complete cardiac evaluation failed to reveal any additional evidence of cardiac toxicity. This patient failed treatment after a total of three courses of AMSA. He remains without any clinical evidence of cardiac abnormalities > 6 months after receiving AMSA.

DISCUSSION

Because of reports of cardiac arrhythmias occurring with AMSA, we began doing frequent ECGs for patients receiving this treatment. The ST-T-wave changes described above were an unexpected finding. We were concerned that they might represent early signs of more severe cardiac toxicity. This fear was not substantiated by extensive cardiac evaluation. The transient nature of the ECG changes may represent a local irritant-like effect on the myocardium. It is unlikely that they represent any true ischemic changes in the heart, in view of normal pyrophosphate studies.

The relationship of our findings to the previously described arrhythmias is not clear. Our ECG abnormalities occurred in the presence of normal potassium and calcium levels and were not associated with rhythm disturbances. It is possible that the ischemic changes in ST-T-waves that we observed could be precursors of serious arrhythmias in the presence of hypokalemia or other metabolic abnormalities. We feel that patients receiving AMSA should continue to have pretreatment and posttreatment ECGs, electrolyte monitoring, and observation for arrhythmias. The presence of transient ECG alterations similar to those we observed should not of themselves be an indication to discontinue therapy with AMSA. Without associated clinical symptoms or evidence of any cardiac rhythm disturbance, treatment with AMSA should be continued in patients whose tumors appear to be responding to this new drug.

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Southwest Oncology Group Experience With Tamoxifen in Metastatic Melanoma

Although epidemiologic, biochemical, and clinical observations have suggested a role for endocrine factors in the growth and spread of malignant melanoma, prospective clinical trials of hormonal therapies in patients with metastatic disease have in general been disappointing. Occasional patients, however, appear to have significant responses to such agents.

Tamoxifen has been tested in metastatic melanoma by at least six investigators (1–6). Analyzed collectively, these studies have yielded a response rate of 10% (partial plus complete responses), lasting a median of 7 months. All of these studies used a fixed dose of tamoxifen ranging from 20 to 40 mg daily.

In 1978, the Southwest Oncology Group initiated a study of melanoma to determine the efficacy of tamoxifen given

with a 7-day loading schedule at 40 mg/m^2 twice a day followed by a fixed dose of 10 mg/m^2 twice a day until disease progression. This schedule was selected in an attempt to overcome any reflex increase in estradiol production following initiation of tamoxifen. Such an increase theoretically may overcome the binding of tamoxifen to steroid receptors on tumor cells. Fabian et al (7) demonstrated that patients treated with this schedule achieved a steady-state blood level 3 weeks earlier than patients treated with the usual schedule of 10 mg orally twice a day.

Twenty-eight patients (20 males and eight females) with metastatic melanoma completed 1 month of prescribed therapy using this loading schedule and were evaluable. All patients had received prior chemotherapy and had measurable disease. Eleven patients (seven males and four females) had tumor biopsied for estrogen-receptor (ER) content; only one had an ER value > 3 fmols/mg.

Tamoxifen in this schedule was well-tolerated. One patient developed mild reversible thrombocytopenia (platelet count, 97,000/mm^3) and another had mild nausea. However, only one patient responded. This was a premenopausal female with ER-negative tumor, who had complete resolution of cutaneous and nodal metastases for 4$^1/_2$ months.

We conclude that this loading schedule does not increase the efficacy of tamoxifen in metastatic melanoma. We cannot share the enthusiasm of others (6) suggesting that tamoxifen be compared to diethystilbestrol in the treatment of metastatic melanoma, since both appear to have only weak antitumor activity in this disease.

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Transplacental Passage of Cyclophosphamide[1]

Cyclophosphamide (CP) is an alkylating agent widely used for the therapy of several solid and hematologic malignancies. The drug is a potent mutagenic substance (1), teratogenic in various animal species including man. The obvious risks connected with the use of cytotoxic drugs such as CP during pregnancy may in some cases be outweighed by the benefits to the mother or to both the mother and the fetus.

This was the case when a 33-year-old pregnant woman (gravida II para 1) at the 25th gestational week was diagnosed as having stage IVB Hodgkin's lymphoma. Because the disease was rapidly progressing by the 29th gestational week, chemotherapy with CP (400 mg/m^2, Days 1–5), vincristine (1.4 mg/m^2, Day 1), and prednisone (100 mg/m^2, Days 1–5) (CVP) was started. Fetal retardation was suspected on the basis of serial ultrasound scans, and at the 34th gestational week amniocentesis was performed to assess fetal lung maturity. The lecithin/sphingomyelin ratio was 3, indicating a "mature" fetal lung. Therefore, a cesarean section was performed at the 35th week; the female infant, weighing 2300 g (in the normal range of Italian fetal growth curves; over the 10th percentile), was well and was discharged at 7 days of life.

As amniocentesis was performed 1 hour after the last iv dose of CP (400 mg/m^2) in the second course of chemotherapy, it was possible to analyze the CP concentration in the amniotic fluid. With the informed consent of the mother, maternal blood samples (1.5 ml) were collected in heparinized tubes before and at intervals during the 24 hours following CP treatment. Plasma was obtained by centrifugation. After double extraction at alkaline pH with ethyl acetate, a previously described gas chromatographic method (2) was applied for CP determination after *N*-trifluoroacetylation, using ifosfamide as internal standard. The original method was modified using a nitrogen phosphorus selective detector.

Figure 1 shows plasma CP levels in the mother and CP concentration in the amniotic fluid. The CP level in am-

[1]Supported in part by a CNR contract in clinical pharmacology and rare diseases by the Italian Association for Cancer Research.

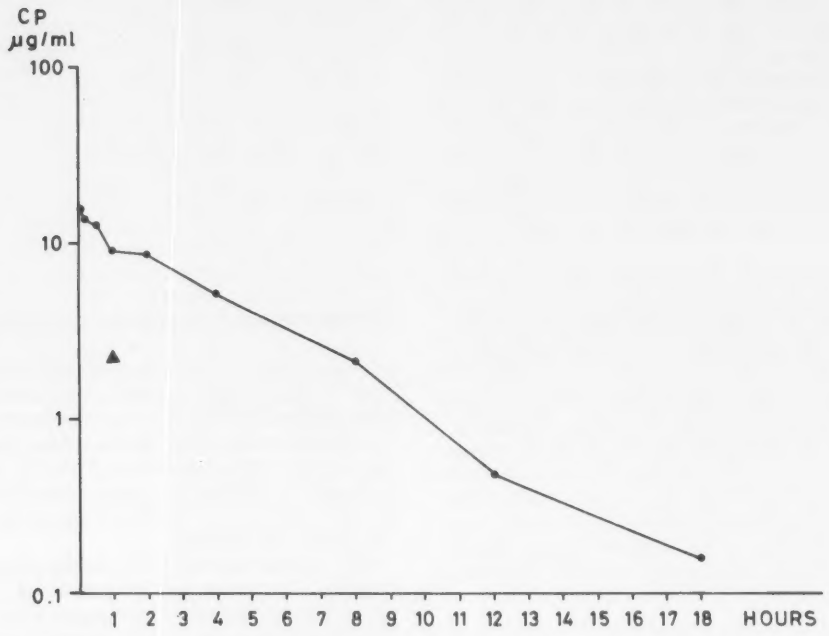

FIGURE 1.—Plasma levels of CP in a pregnant woman given 400 mg/m², iv (●). CP in amniotic fluid of the same patient 1 hr after drug administration (▲).

niotic fluid (2.1 µg/ml) was considerable, amounting to approximately 25% of the plasma level at the same time. The disappearance of CP from plasma fits a biexponential pattern of decay as already described for nonpregnant women (3,4). The elimination half-life was 146 minutes, slightly less than previously reported (3,4); the volume of distribution was 0.78 liters/kg, in agreement with previous data (3,4).

As far as we know, this is the first report of transplacental passage of CP. The finding could have considerable practical implications, considering that fetal liver microsomal enzymes contain a P-450-dependent mono-oxygenase system (5) and therefore can presumably activate CP to the mutagenic and cytotoxic metabolites hydroxycyclophosphamide, aldophosphamide, and phosphoramide mustard.

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Aclacinomycin A Flare

In an article in the November/December 1979 issue of *Cancer Treatment Reports* (vol 63, pp 2067–2069), Nicholas J. Vogelzang described an "Adriamycin (doxorubicin) flare" skin reaction that occurred in 3% of 100 consecutive patients observed. At the Ohio State University Hospital, a similar reaction has been observed in one patient receiving aclacinomycin A, a phase I drug similar to doxorubicin in structure (1). This one occurrence of a flare reaction is the only one of its kind noted after 110 administrations of aclacinomycin A to 54 patients at Ohio State University Hospital.

The aclacinomycin A flare was noted in a 67-year-old white female with metastatic gastric carcinoma. She had received previous chemotherapy with 5-FU, doxorubicin, and mitomycin (October 1979 to April 1980) and with two courses of AMSA (October 1980); the flare reaction occurred during her sixth course of treatment with aclacinomycin A. She had had no previous reactions to past doses of aclacinomycin A ranging from 90 mg to 162 mg and had had a total dose of 572 mg in previous treatments. The sixth course of aclacinomycin A given on June 25, 1981, was her last. She died 10 days later of respiratory arrest.

The clinical nurse specialist administering the drug started an iv infusion of 5% dextrose in water with a 23-gauge scalp vein butterfly needle in the median vein of the right forearm. The patency of the line was documented before, during, and after the administration of the drug by occlusion of the vein proximal to the needle and by observation of a good blood return on aspiration with a syringe and needle inserted through the bulb of the iv tubing. The patient was instructed to report any pain or discomfort at the venipuncture site while 90 mg of aclacinomycin A was given by slow iv push into the continuously flowing iv infusion of 5% dextrose in water. The drug was administered in approximately 10 minutes. About 5 minutes into the infusion, the patient complained of a stinging sensation about 4 inches proximal to the venipuncture site. The nurse then slowed the pushing of the aclacinomycin A and allowed longer intervals of flushing the line with 5% dextrose in water. The stinging lessened somewhat but persisted throughout the rest of the infusion. There were no physical changes noted at the location of the stinging sensation. No redness, swelling, pain, or other discomfort was experienced at the venipuncture site. However, after the aclacinomycin A had been administered, some red, nonraised blotches began to appear along the vein from the venipuncture site to the area where the patient had complained of the stinging. The infusion of 5% dextrose in water was continued at the full rate, and a heat lamp was placed over the affected area (this is our oncology unit's usual procedure with vein irritation from drugs). The stinging stopped shortly, but it took about 1 hour before the red blotches subsided and finally disappeared completely.

In conclusion, it appears that aclacinomycin A may cause a flare reaction similar to that of doxorubicin.

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Leukemia Occurring After Treatment of Small Cell Lung Cancer [1]

Since the advent of effective combination chemotherapy, the median survival of patients with small cell carcinoma of the lung has reached 10–12 months. Few patients, however, survive beyond 2.5 years (1). Between 1974 and 1978, 40 patients at the University of Minnesota were treated with lomustine (CCNU)- and doxorubicin-containing regimens (2). One patient survived 5 years, and he has developed acute leukemia.

CASE REPORT

This 56-year-old white male smoker was well until December 1976, when he developed chest pain, cough, and hoarseness. Bronchoscopy revealed a fungating tumor mass extending distally from the lateral wall of the left main stem bronchus. Pathologic review at the University of Minnesota confirmed the diagnosis of small cell anaplastic carcinoma. The physical examination was normal. The chest X-ray disclosed a left upper lobe infiltrate and a left hilar mass. The gamma glutamyl transferase was slightly elevated, but the liver and spleen scan was normal. The level of carcinoembryonic antigen was elevated (17 ng/ml) at the start of therapy. The bone marrow examination was normal except for increased iron stores. The HLA type was A2A3 B7BW15.

Chemotherapy was begun on December 31, 1976. The patient received 100 mg/m^2 of CCNU, 50 mg/m^2 of doxorubicin, 1 mg/m^2 of vincristine, and 100 mg/m^2 of pro-

[1]Supported in part by Public Health Service grant CA-19527 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; by American Cancer Society Junior Faculty Fellowship JFCF 639 to N. J. Vogelzang; by the Minnesota Medical Foundation; and by the Masonic Memorial Hospital Fund, Inc.

carbazine orally daily for 14 days. After the first course of chemotherapy, the chest radiograph was normal. The patient was treated with identical doses of drugs on February 11, 1977, and March 29, 1977. During the fourth course of chemotherapy beginning May 15, 1977, he received 4000 rads via a 10 MeV linear accelerator to the mediastinal, hilar, and left upper lobe areas. He also received 120 mg of CCNU and 2 mg of vincristine coincident with the radiotherapy. The patient received chemotherapy in varying doses until November 6, 1978. By that time he had received a total of 870 mg of doxorubicin, 1300 mg of CCNU, 17 mg of vincristine, and 14 g of procarbazine.

The patient was observed after completion of therapy, and progressive thrombocytopenia was noted. In January 1981, the platelet count was 91,000/μl. On September 28, 1981, a platelet count of 17,000/μl, easy bruisability, and recurrent skin infections were noted. The peripheral wbc count was 3200/μl, with 3% blast cells, 52% neutrophils, 18% lymphocytes, 25% monocytes, and 2% eosinophils. The hemoglobin was 11.2 g/100 ml. The carcinoembryonic antigen level was normal. The bone marrow examination revealed dyserythropoiesis, ringed sideroblasts, decreased megakaryocytes, and 16% myeloblasts. The blast cells were large, with variable amounts of cytoplasm and myeloperoxidase-positive granules. No Auer rods were seen. The morphology of these blast cells was consistent with the M2 subtype of acute leukemia using the French-American-British classification.

G-banded chromosomes were analyzed in 23 cells from direct preparations and 24-hour cultures of bone marrow. Six cells showed a normal 46, XY male karyotype. The remaining 17 cells had a modal number of 46 chromosomes with a duplication of the long arm of one No. 12 chromosome as the only abnormality: 46, XY, dup (12) (q 12→q 24).

The patient elected to have only transfusion therapy. Since the diagnosis of leukemia, he has required eight to 16 HLA-matched donor platelet packs per week. He has had no infections and has not required rbc transfusions. A repeat bone marrow on December 14, 1981, disclosed 15.8% myeloblasts.

DISCUSSION

Patients with small cell lung cancer who are long-term survivors after intensive multimodality therapy appear to be at risk for treatment-related leukemia (3,4). The degree of risk is unclear. Hansen et al (5) have not observed any treatment-related leukemia in 16 long-term survivors of multimodality treatment. Matthews et al (1) reported no cases of chemotherapy-related leukemia in 46 patients followed for > 2.5 years. Bradley et al (4) reported on eight long-term survivors, one of whom developed erythroleukemia. Multiple cytogenetic abnormalities were found in the malignant blast cells.

Specific chromosome abnormalities that have been reported to be associated with treatment-induced acute leukemia include partial deletion of the long arm or complete loss of chromosomes 5 and 7 (6). The significance of the duplication found in this patient is unknown.

Finally, the occurrence of acute leukemia in this and other patients should stimulate a reappraisal of the dose, schedule, and role of leukemogenic agents such as CCNU, procarbazine, radiotherapy, and alkylating agents in the treatment of small cell lung cancer. The length and intensity of induction therapy need close scrutiny, and agents with less leukemogenic potential, such as etoposide and doxorubicin, should find wider use.

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ANNOUNCEMENTS

Multidisciplinary Approach to Management of Patients With Mesothelioma

East Lansing, Michigan, September 16–17, 1982

This international workshop is sponsored by The International Association for Study of Lung Cancer and the Michigan State University, in cooperation with the Ingham Medical Center. A practical multidisplinary approach to the management of patients with malignant mesothelioma will be outlined, and a master protocol for the collection of data on environmental factors and treatments associated with particular patients will be designed. A line of communication for exchange of information between participating investigators will also be planned.

The number of participants is limited.

For further information, contact: M. A. Hollandsworth, Asbestos-Mesothelioma Program, 405 W Greenlawn Ave, Suite 330, Lansing, MI 48909. Telephone (517) 374-2107.

Urologic Cancer Course

Boston, Massachusetts, September 22–24, 1982

This intensive 3-day course, to be held at the Parker House Hotel, will provide an overview of the clinical and pathophysiologic basis for the diagnosis and treatment of patients with urologic cancer. The course will emphasize the multidisciplinary approach that constitutes the foundation of contemporary care for patients with urologic cancers. Principles derived from the disciplines of urologic surgery, medical oncology, and radiation therapy will be highlighted and incorporated into a comprehensive consideration of therapeutic practices. Although teaching will be primarily provided through lectures, panel discussions addressing major current controversies in urologic cancer will be an integral portion of the course. A comprehensive syllabus will be provided.

Guest faculty will include Drs. Lawrence H. Einhorn, Donald Skinner, Willet F. Whitmore, Jr, and Leonard Zinman. The Harvard faculty participants will include leaders in urologic cancer from the Sidney Farber Cancer Institute, Brigham & Women's Hospital, Joint Center for Radiation Therapy, Children's Hospital Medical Center, Beth Israel Hospital, and Massachusetts General Hospital.

The course fee is $325.00

For further information contact: Harvard Medical School, Department of Continuing Education, Boston, MA 02115 (617-732-1525).

Cancer and Nutrition, an Oncology Update at the 15th Annual Malignant Disease Symposium

Chapel Hill, North Carolina, October 22–23, 1982

The Clinical Oncology Education Program and the Cancer Research Center at the University of North Carolina School of Medicine at Chapel Hill will sponsor this 2-day symposium. It will cover the mounting evidence from current epidemiologic and clinical research studies that points to an association of nutrition with certain cancers and how new preventions and treatments against these cancers are being tested as a result of these studies. In addition, new techniques for feeding by mouth, tube, and vein and how they are changing the management of cancer patients will be discussed.

This symposium has been organized to bring the most up-to-date information about these developments to practicing physicians, house staff, nurses, and health professionals involved with cancer patients.

The registration fee is $125; the symposium offers 12 credit hours, Category 1 AMA-PRA.

For further information, contact: William D. Heizer, MD, Cancer Research Center, Box 30, MacNider Bldg, Chapel Hill, NC 27514.

Paraneoplasia: Basic Concepts and Clinical Aspects

Brussels, Belgium, November 5–6, 1982

This 2-day symposium presented by the European Organization for Research on Treatment of Cancer will focus on endocrine paraneoplasia, neurologic paraneoplasia, coagulopathies, and nonhormonal tumor markers. The Chairmen are J. Waldenström and H. J. Tagnon.

In addition, free communications of 10 minutes each will be accepted. An abstract must be sent to the address below before September 30, 1982. Seating is limited and preregistration is recommended.

For further information, contact: Dr. M. Staquet, Director, EORTC Data Center, rue Héger-Bordet 1, 1000 Brussels, Belgium. Telephone: (2) 538.57.90, Telex: 22773.

Second Winter Symposium on Hematologic Malignancies

Snowbird, Utah, February 12–19, 1983

This symposium will feature a multidisciplinary faculty from the University of Arizona Cancer Center. They will review recent diagnostic and therapeutic advances in the lymphomas, leukemias, and multiple myeloma.

For further information, contact: Stephen E. Jones, MD, Section of Hematology and Medical Oncology, University of Arizona Cancer Center, Tucson, AZ 85724.

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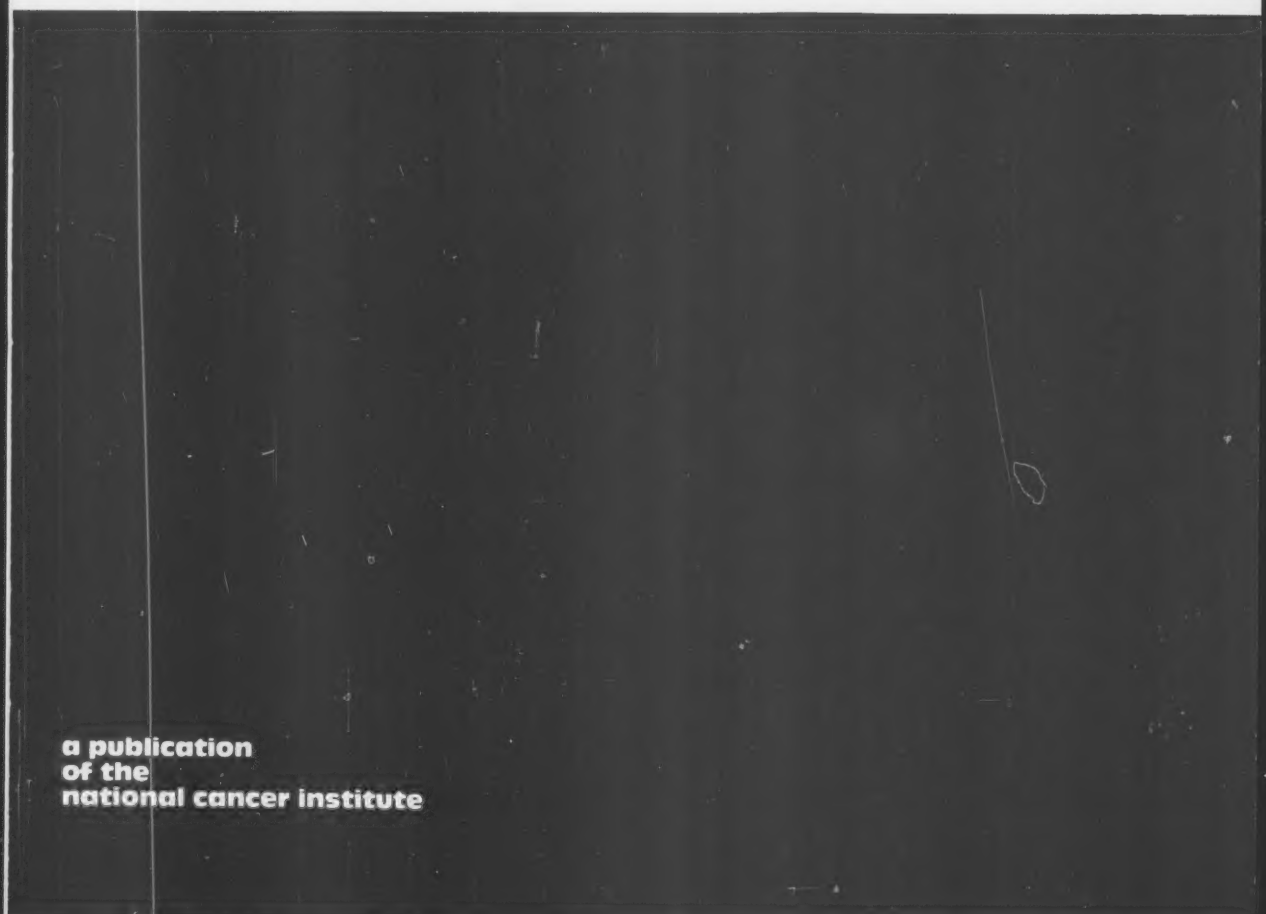

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